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A Microglia Initiated Target Therapy in Neuroinflammation for Alzheimer's Patients

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Abstract

The research is focused on neuroinflammation a normal physiological process which is known to be associated with neurodegenerative diseases could be the potential targeted therapy via the microglia cells, it starts with defining Alzheimer's; a neurodegenerative disease which causes deposition of Aβ (amyloid beta) protein in the cerebral cortex as well as NFT (neurofibrillary tangles) in the hippocampus and basal ganglia. The paper then describes process of neuroinflammation, microglia's role, apolipoprotein E4 gene in relation to Alzheimer's, which leads to different stem cell research and how pruning microglia as well as targeting microglia receptors in the brain is being used in current research trials, we included multiple meta-analysis showing microglia receptors being targeted currently by emerging drugs like propofol, antibodies CSF1R inhibitor etc, which are currently under trial phase, the research ends with concluding potential diagnostic markers like sirt1 considered to be an anti-aging protein which can be used as therapeutic interventions and Lps effect on Sirt 1.

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Alzheimer's disease and its effect on people

Epidemiological effect

The most frequent reason for a loss in cognitive capacity is Alzheimer disease (AD). It is a neurological condition involving language, memory, understanding, attention, judgment, and reasoning that often affects persons over the age of 65. (29) In the US, it is the sixth most common cause of death. Less than 10% of Alzheimer's patients have early onset, which is rare and occurs before the age of 65. There may be 24 million dementia sufferers worldwide, and by 2050, that number is expected to have multiplied four times. Alzheimer's disease is thought to cost the US healthcare system $172 billion annually. (29).

Risk factors

Both early-onset Alzheimer's disease and late-onset Alzheimer's disease have a genetic component. A risk factor for dementia with early onset is trisomy 21.

Alzheimer's disease has been linked to several risk factors. The main risk factor for Alzheimer's disease is getting older. Alzheimer's disease risk factors include traumatic brain injury, depression, cardiovascular and cerebrovascular illness, older parental age, smoking, a family history of dementia, elevated homocysteine levels, and the presence of the APOE e4 allele. The likelihood of getting Alzheimer's increases by 10% to 30% if you have a first-degree relative who has the illness. The chance of developing Alzheimer's disease is three times higher in people with 2 or more siblings who have the condition than in the general population. The risk of Alzheimer's disease is known to be reduced by higher education, estrogen use by women, anti-inflammatory drug use, leisure activities like reading or playing an instrument, a good diet, and regular aerobic exercise. (44) (33).

Pathophysiology of AD

Studies on etiology of the disease shows that overproduction and poor clearance of beta-amyloid are thought to cause AD. Tau hyperphosphorylation and neuronal toxicity are subsequent events. The three main pathologic characteristics of AD are extracellular -amyloid deposition in the form of neurotic plaques, intraneuronal tau protein deposition in the form of intraneuronal neurofibrillary tangles, and brain atrophy from localized neuronal and synaptic loss. In the cerebral blood vessels, amyloid also accumulates. The severity of cerebral amyloid angiopathy varies from minor deposits of amyloid to significant accumulations that alter the architecture of the arteries and result in microinfarcts, microaneurysms, and cerebral microhemorrhages (2). The microscopic lesions known as plaques are spherical and contain an extracellular amyloid beta-peptide core encircled by enlarged axonal endings. The transmembrane protein known as an amyloid precursor protein (APP) is the source of the beta-amyloid peptide. Alpha, beta, and gamma-secretases act as proteases to cleave the beta-amyloid peptide from the APP. The tiny fragments of APP that are produced when either alpha-secretase or beta -secretase cleaves it are typically not toxic to neurons; However, the beta-secretase and gamma-secretase cleavages in succession produce 42 amino acid peptides (beta-amyloid 42). Amyloid aggregation, which results in neuronal toxicity, is caused by an increase in beta-amyloid 42 levels (29).

Other genetic risk factors

There are other genetic risk factors that are related to AD. TREM2, APOE, CLU, SORL1, BIN1, and PICALM are additional genes with known variants linked to an increased risk of Alzheimer's disease. Apolipoprotein E (APOE), a protein involved in fat metabolism, and its E4 allele are the most prevalent genetic risk factors for AD, with an allele frequency of 13.7%. Heterozygosity for this allele increases the risk by threefold. TREM2R47H (triggering receptor expressed on myeloid cells 2) has a similar effect size despite being less common. The association between inflammation and AD pathogenesis is supported by TREM2, a receptor that is expressed on various immune cell types (Sheppard & Coleman, 2020).

Symptoms of AD

Alzheimer's disease is initially only known to cause memory loss, but over time, the patient may experience severe cognitive and behavioral symptoms like paranoia, depression, anxiety, and anger (29). Most of them will need assistance with activities of daily living as the disease worsens. In time, even walking becomes challenging, and many people may not be able to eat or experience swallowing issues that result in aspiration pneumonia. The amount of time between diagnosis and death varies; some people may pass away within five years, while others may live for ten years. However, overall, the quality of life is very bad. Although an interprofessional approach to the management of Alzheimer patients is advised, an analysis of several studies shows that this approach has no bearing on the care of

his patients. But in order to ascertain what kind of strategy is most effective for treating these patients, more thorough studies will be needed due to the heterogeneity in the earlier studies; However, this research is trying to review deeper in neuroinflammatory pathophysiology correlated to microglia to hopefully can help with better management of the disease.

Neuroinflammation

General background of neuroinflammation

By eliminating or inhibiting various pathogens, neuroinflammation serves as a first line of defense for the brain (Wyss-Coray, & Mucke, 2002 as cited in (30). Through the stimulation of tissue repair and the removal of cellular waste, this inflammatory response can be advantageous. But persistent inflammatory responses are bad because they prevent regeneration. The persistence of inflammatory stimulation can be brought on by internal (e. g., protein aggregation and genetic mutation) or environmental (e. g., drugs, trauma, and infections) factors. Microglia and astrocytes participate in the ongoing inflammatory responses, which can result in neurodegenerative diseases (30). The central nervous system is composed primarily of neurons and glial cells. Since glial cells don't generate electrical impulses, they were once thought of as the support cells for neurons. In terms of cellular variety and function, it has been found that glial cells outperform neurons (30).

According to the traditional theory, AD amyloid plaques are surrounded by reactive gliosis and activated microglia, which define neuroinflammation (24); (8) as cited in (25). This approach views neuroinflammation as a passive response to tau protein and amyloid plaque. Recent research suggests neuroinflammation precedes the typical AD characteristics, making it the third pathological hallmark of AD and contributing to its pathogenesis (11) as cited in (25).

Microglia's role in neuroinflammation

Neuronal activity can be regulated by glial cells like oligodendrocytes, microglia, and astrocytes. Innate immune responses are one of the many functions performed by microglia and astrocytes in the brain. The M1 (classical activation) and M2 (alternative activation) phenotypes of microglia are separated based on their level of activation (30). Microglia using their senses, which are encoded by various genes, they can first detect changes in their environment. The second is the bodily housekeeping process, which entails moving to injured areas, remodeling synapses, and preserving myelin homeostasis. The third involves defense against harmful stimuli, such as damage- and pathogen-associated molecular patterns (PAMPs) and DAMPs. The toll-like receptors (TLRs), nuclear oligomerization domain-like receptors (NODRs), and viral receptors, which are expressed on microglia and can detect PAMPs and DAMPs, are examples of cellular receptors. In response to these stimuli, microglia release chemokines like C-C motif chemokine ligand 2 (CCL2) and IL-18, as well as proinflammatory cytokines like tumor necrosis factor (TNF)-, interleukin (IL)-1, and IL-16 to attract additional cells and clear pathogens (30). Neuroinflammation is a neuroprotective mechanism, but it can also be neurotoxic and linked to neurodegeneration if it persists for an extended period of time. Additionally, microglia priming with aging and ongoing stress exhibits dystrophic morphology and an exaggerated inflammatory response (30).

Depending on their level of activation, microglia in the central nervous system (CNS) can be either pro-inflammatory or neuroprotective. Pro-inflammatory cytokines, which are byproducts of pathogens or damaged cells, cause resting microglia to express pro-inflammatory molecules like IL-1, TNF-, IL-6, nitric oxide (NO), and proteases, which are harmful in neurodegenerative diseases. Contrarily, IL-4,

IL-10, IL-13, and transforming growth factor (TGF) activate neuroprotective microglia and cause the release of a variety of proteins, including FIZZ1, Chitinase-3-Like-3 (Chi3l3), Arginase 1, Ym1, CD206, insulin-like growth factor (IGF-1), and Frizzled class receptor 1 (Fzd1). These microglial proteins may be involved in tissue repair and neuro (30).

Apolipoprotein E4 role in Neuroinflammation

Numerous innate immune-related genes have been linked to an increased risk of developing neurodegenerative disorders by genome-wide association studies (GWAS), indicating that immune cells are important in the pathogenesis of neurodegeneration. Apolipoprotein E (APOE), a gene, is among those with disease-related variants. Apolipoprotein E4 (APOE4) allele is a significant shared risk factor for a number of neurodegenerative diseases, including Alzheimer's disease (AD), and APOE2 allele lowers risk for AD. Due in part to its function in lipid metabolism and associated inflammation, APOE4 is also the strongest genetic risk factor for developing late-onset AD. Comparing APOE4 carriers to non -carriers, APOE4 carriers in AD exhibit earlier A-plaque deposition and clinical disease onset, as well as quicker disease progression, a heavier burden of A-plaques, and increased brain atrophy, highlighting a significant role for APOE4 in AD pathogenesis. Comparatively to non-APOE2 carriers, APOE2 carriers have later A deposition, clinical onset, and increased longevity. Although there are currently some hints as to the cause(s) of AD, there is still much that is not fully understood (48). APOE plays a crucial role at the intersection of inflammation and neurodegeneration via glial-mediated mechanisms, in addition to clearance of or response to misfolded proteins, such as Amyloid and tau (48). Leukocytes and hepatocytes, particularly a type of resident hepatic macrophage known as Kuppfer cells, are the primary sources of ApoE expression in the periphery while astrocytes and disease-associated microglia (DAM) are the primary producers of ApoE in the CNS (48). Studies indicate that the two sources and metabolism of each pool of ApoE work separately from one another, despite the fact that the peripheral role of ApoE in AD has not been studied as thoroughly as that of the CNS (48). Learning and memory deficits seen in global ApoE KO mice are rescued by genetically restoring peripheral ApoE expression in those mice [94], suggesting that peripheral ApoE may affect CNS functions via the vasculature. According to APOE4 carriers who have elevated levels of the proinflammatory cytokines IL-8 and TNF after cardiopulmonary bypass surgery, APOE4 is also linked to an increased inflammatory response in the periphery, like the CNS (48). Furthermore, APOE4 carriers had an increased risk of AD with earlier disease onset. This association was also true for peripheral chronic low-grade inflammation (48).

These studies demonstrate the diverse roles played by APOE4 in systemic inflammation in general and in AD, and they hypothesize that the APOE4 allele can influence AD pathology by altering the inflammatory response. How APOE4 interacts with immune cell activity to cause neurodegeneration associated with AD remains a crucial open question

Stem cell therapy directed towards the inflammatory factors

General use of stem cell therapy

Utilizing stem cell technologies for drug development, disease modeling, and cell therapies has garnered more interest in recent years (38); (31) Yang et al., 2020 as cited in Si & Wang, 2021). Induced pluripotent stem cells (iPSCs), neural stem cells generated from the brain (NSCs), and bone marrow mesenchymal stem cells are the stem cell types most frequently used in AD research (MSCs) (Yang et al., 2013; (9), (49) as cited in Si & Wang, 2021). Traditional therapies may not be as effective as stem cell-based therapy since it has the potential to enhance the microenvironment of the brain

fundamentally, boost synaptic connections, and prevent neuronal loss. Some of the mechanism of action of targeted stem cell therapy include.

1. Replacement of damaged or lost neuronal cells: Cholinergic neurons, which can differentiate from stem cells and integrate with the host, remodel brain circuits, and soon replace the missing neurons, can be produced by stem cells (Telias and Ben-Yosef, 2015 as cited in Si & Wang, 2021).
2. Neurotrophic factor secretion: To encourage cell survival, boost synaptic connections, and enhance cognitive function, stem cells can release neurotrophic factors such brain-derived neurotrophic factor (BDNF) and fibroblast growth ((6) as cited in Si & Wang, 2021).
3. Production of anti-amyloid proteins: Stem cell transplantation lowers levels of amyloid beta (A) and lowers toxic responses to A, which is advantageous again for survival of transplanted cells and cognitive recovery ((3) as cited in Si & Wang, 2021).
4. Anti-inflammatory response: stem cell transplantation reduces the expression of proinflammatory factors interleukin-1β, interleukin-6, tumor necrosis factor-α, inducible nitric oxide synthase, and exerts neuroprotective effects (35) as cited in Si & Wang, 2021).
5. Promotion of endogenous stem cell activation: Exogenous stem cell transplantation enhances the brain's microenvironment, allowing endogenous stem cells to survive and be activated (50) as cited in Si, & Wang, 2021).
6. Enhancement of the metabolic activity of brain neurons: stem cell transplantation boosts neural connectivity and metabolism, which enhances cognitive performance ((7) as cited in Si, & Wang, 2021).

The ability of stem cells to multiply, regenerate, and divide into multiple mature cell lineages defines them. Embryonic stem cells (ESCs) induced pluripotent stem cells (iPSCs), mesenchymal stem cells (MSCs), and neural stem cells are among the various types of stem cells (NSCs). The categorization is based on a variety of cell types that may be produced and derived (Sivandzade & Cucullo, 2021).

Use of Mesenchymal cells

The most often employed stem cells in therapeutic studies for AD are mesenchymal stem cells (MSCs). (19) made the initial discovery of mesenchymal stem cells or mesenchymal stromal cells (25). MSCs play a role in the growth of many mesenchymal tissue types and can be extracted from umbilical cord blood (UCB-MSCs) or Wharton's jelly. They can also be found in bone marrow and adipose tissue, among other adult stem cell habitats (15). Mesenchymal stem cells offer a number of benefits: In comparison to ESCs and NSCs, MSCs have the following advantages: (i) they are not associated with any complex ethical issues; (ii) they are simple to obtain, manipulate, and store; (iii) they nearly express no HLA antigen, allowing allogeneic transplantation to be accomplished without immunosuppression; (iv) they are far less likely to develop tumors; and (v) MSCs can modulate immune response and reduce neuroinflammation in AD. MSCs are currently the most commonly used stem cell source in AD regeneration therapy because to their adaptable qualities (25). They have three key functions in treating AD: controlling the immune system, reducing the amount of Amyloid plaques by internalizing and degrading endosomal-lysosomal pathway oligomers, and having neurotrophic/regenerative potential (18).

Currently, the widespread consensus is that transplanted MSCs primarily work through paracrine mechanisms (Walker & Jucker, 2015;(15) ;(22); (36) as cited in (25). Mesenchymal stem cells secrete numerous neurotrophic and angiogenic factors through paracrine action, including glial cell derived

neurotrophic factor (GDNF), vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), insulin growth factor (IGF), and others, as demonstrated by our research and that of others. The milieu for the remaining neurons in the sick location may be improved by such neurotrophic and angiogenic substances, which may also encourage neuronal regeneration and repair. Intranasal delivery of the secretome obtained by MSCs subjected in vitro to AD mouse brain homogenates (MSCCS) has recently been shown to produce lasting memory recovery, together with a marked decrease in the amount of amyloid plaque and reactive gliosis, in APP/PS1 AD mice. Additionally, they discovered that MSC-CS-treated APP/PS1 mice had healthier conditions than vehicle-treated mice, as seen by larger neuronal densities in the cortex and hippocampus, which were linked to a decrease of hippocampal shrinkage and a longer lifetime. This suggests that MSC-derived secretome can be used to mimic the beneficial effects of MSC transplantation in AD, including improvements in memory, amplified amyloid plaque removal, reduced neuroinflammation, and enhancement of endogenous neurogenesis. This strongly suggests that perhaps the paracrine effects of MSCs play a crucial role in MSC transplantation studies (54), as cited in (25). Modulation of neuroinflammation is a key component of the MSCs treatment mechanism. As was already noted, neuroinflammation is crucial to AD etiology. Mesenchymal stem cells have been proven in numerous studies to change microglia and astrocytes from pro-inflammatory M1 and A1 phenotypes to anti-inflammatory M2 and A2 phenotypes, thereby reducing the neuro - inflammatory response and neuronal damage in AD (Wei et al., 2018; Zhao et al., 2018; (52) as cited in (25). In a different study it was found that after (Adipose-derived mesenchymal stem cells) ADSC transplantation in the cerebral of APP/PS1 transgenic mice, studies showed that the result was decreased amount of β amyloid (Aβ) which increased cognitive function and memory, it was also found that activated microglia predominately surrounded and penetrated plaques in both the hippocampus and the cortex. The expression levels of anti-inflammatory were increased whereas pro-inflammatory factors decreased, as well as A-degrading enzymes, were higher in the activated microglia, demonstrating an activated phenotype. According to these findings, MSC transplantation can slow cognitive impairment in AD mice by preventing neuroinflammation mechanisms (39). The MSCs may potentially target the recognizable traits of the traditional AD. Numerous research using MSC transplantation in AD transgenic mouse models have revealed lower tau hyperphosphorylation and A plaque load (43); Zhao et al., 2018; (54) as cited in (25). MSC's which are umbilical cord derivatives tend to secrete Soluble intracellular adhesion molecule-1 (Sicam-1) which stimulates release of neprilysin which is an alpha beta degrading enzyme and hence gets clear of the plaques, via internalization and degradation of the endosomal-lysosomal pathway, MSCs can further lower the load of plaque. By speeding overall clearance of amyloid and tau, MSC transplantation has been proven in animal tests to relieve the symptoms of AD rats (27) as cited in (25).

Anti- aging gene Sirtuin 1

Apoptosis occurs later in life in certain brain regions, but it may not affect neurons in the appetite center in neurodegenerative diseases like Parkinson's disease (PD) and Alzheimer's disease (AD). Insulin resistance and dysregulated appetite are now closely linked to neurodegenerative diseases like Parkinsons and Alzheimer's disease (AD), which have become the main focus of brain research. Food intake disorders are caused by early neuron transcriptional dysregulation involving the SCN, and it cannot be ruled out that early defects in neurons within the appetite center occur in populations worldwide with appetite dysregulation linked to neurodegenerative diseases like PD and AD. Sirtuin 1 (Sirt 1), an anti-aging gene linked to circadian rhythm and effects on endocrine and metabolic systems, including diseases of the adipose tissue, heart, liver, pancreas, and brain, is linked to appetite

dysregulation. Sirtunin 1 and other anti-aging genes control neuron apoptosis and survival. Interventions that stop the downregulation of anti-aging genes may enable appetite regulation and prevent the development of other chronic diseases. Early intervention has been necessary due to the rise in non-alcoholic fatty disease (NAFLD) in populations worldwide, which is linked to the severity of conditions like obesity, diabetes, and neurodegenerative diseases. The goal of delaying and preventing programmed cell death associated with the different chronic diseases has prompted increased interest in calorie restriction combined with stabilization of anti-aging genes in recent years. Abnormal post-prandial lipid metabolism is a component of diet and lifestyle interventions in chronic diseases like obesity, diabetes, and cardiovascular disease.

Nutrition has a strong correlation with insulin and insulin-like growth factor-1 (IGF-1), which in turn has a correlation with genotoxic stress, mitochondrial apoptosis, cell senescence, and neurodegeneration worldwide.

With the newfound understanding that may postpone early pathways in cells that lead to programmed cell death, interest in genomics that results in the discovery of novel genetic pathways aids in the treatment of a variety of chronic diseases. Low-calorie diets that regulate nutrition show that Sirt 1 maintains its connections with other anti-aging genes like Klotho, p66Shc (longevity protein), and FOXO1/FOXO3a. These genes have been linked to cell death through effects on the metabolism of glucose, lipids, and amyloid beta. The degree of endocrine and metabolic disorders is linked to early neuronal transformation and poor neuron survival, which causes appetite dysregulation and overeating, which is linked to metabolic disease.

Diets that regulate the absorption of bacterial lipopolysaccharides (LPS) are essential for preventing neurodegeneration and non-alcoholic fatty liver disease (NAFLD), and it's possible that LPS accelerates appetite dysregulation and chronic diseases by suppressing anti-aging genes. LPS may also have an adverse effect on IGF-1-mediated anti-aging gene expression, since IGF-1/p53 transcriptional regulation is connected to Sirt 1 regulation of cell survival in stressed and aged cells. To alleviate dysregulation of appetite. Diets that regulate the absorption of bacterial lipopolysaccharides (LPS) are essential for preventing neurodegeneration and non-alcoholic fatty liver disease (NAFLD), and it's possible that LPS accelerates appetite dysregulation and chronic diseases by suppressing anti-aging genes. LPS may also have an adverse effect on IGF-1-mediated anti-aging gene expression, since IGF-1/p53 transcriptional regulation is connected to Sirt 1 regulation of cell survival in stressed and aged cells. To alleviate dysregulation of appetite.

Maintaining an appetite helps the endocrine and metabolic system, which is linked to disorders of the blood-brain barrier (BBB) and other organ systems. as well as stop overeating, which has been connected to stress and gene-environment effects on metabolic disease. Early in life, the apelinergic pathway must be maintained. The regulation of appetite is influenced by nitric oxide (NO), and disruptions in NO levels have been linked to a number of chronic illnesses. High-NO diets override Sirt 1-regulated cell NO maintenance, which is relevant to thrombosis, metabolic diseases, and endocrine disorders. Numerous neuropeptides, including brain-derived neurotrophic factor (BDNF) and NPY, hormones, including insulin, adiponectin, and leptin, and intestinal peptides have all been linked to the regulation of appetite. Since the repression of these genes does not maintain the action of the various neuropeptides, hormones, and intestinal factors that govern appetite regulation with relevance to chronic diseases, the role of zinc and Sirt 1 in the regulation of anti-aging genes has become important. An individual's survival against autonomous disease caused by the environment (bacterial

lipopolysaccharides, drugs, xenobiotics) in various communities is improved by anti-aging therapy that preserves appetite regulation.

Changes in gene expression and aberrant post-transcriptional regulation, which are closely linked to appetite dysregulation, modify the anti-aging genes involved in appetite regulation in Suprachiasmatic nucleus SCN neurons within the brain. Maintaining circadian rhythms requires the synchrony of neurons in the (SCN), and disruptions in this synchrony are linked to autonomous neuron disease, which is linked to liver dysfunction and the repression of anti-aging genes. Sirtuin 1 (Sirt1) is the gene that controls how much food is consumed. It has been connected to obesity, cardiovascular disease, and a longer life span. It also affects energy metabolism, inflammation, NAFLD, mitochondrial biogenesis, neurogenesis, glucose/cholesterol metabolism, and amyloidosis. Sirt1 is necessary for neurogenesis, and calorie restriction activates it. Sirt1 affects longevity by modifying the pathways involved in phosphoinositide 3 kinase and the cardiovascular changes that come with aging. Forkhead box protein O1 (FOXO1) deacetylation (apoptosis), which involves p53 transcriptional dysregulation and peroxisome proliferator activated receptor (PPAR) gamma nuclear receptor, is connected to the regulation of glucose. Moreover, interactions between Sirt and p53 may control immune responses and adipocytokines, which may be crucial for NAFLD, obesity, and neurodegeneration.

The regulation of appetite, calorie restriction, and neurodegeneration involving Sirt 1 mediated regulation of other anti-aging genes, such as p53 and FOXO deacetylation, have garnered attention in relation to independent liver and brain diseases. Within these tissues, Sirt 1 plays a crucial role in the upkeep of the mitochondria and the deacetylation of the transcriptional factor FOXO3a, which suppresses the expression of the Rho-associated protein kinase-1 gene. This, in turn, activates the non-amyloidogenic α-secretase, which processes the amyloid precursor protein, thereby reducing the generation of amyloid beta (Aβ) in neurons.

The anti-aging genes (Sirt 1, Klotho, p66Shc (longevity protein), FOXO1/FOXO3a) linked to IGF-1 and cancer, and amyloid beta interactions with aberrant p53 transcriptional regulation are all associated with transcriptional regulation of Sirt 1/p53. (77).

With changed astrocyte-neuron interactions and early programmed cell death, neurons in the brain with Sirt 1 repression may age more quickly. The SCN is affected by Sirt 1 and its brain dysfunction, and Sirt 1 repression deactivates the SCN, which is responsible for controlling appetite, blood glucose levels, the circadian rhythm, and the metabolism of xenobiotics in the liver. The processing of the amyloid precursor protein (APP) to decrease amyloid beta generation involves Sirt 1 activation of the non-amyloidogenic α-secretase. Increased toxic amyloid beta formation linked to mitochondrial apoptosis was caused by Sirt 1 dysregulation.

The apelinergic pathway and fibroblast growth factor 21 are regulated by Sirt 1, and these processes are linked to brain insulin resistance (stroke, dementia, AD). The relationship between NO and epigenetics and how it relates to human health and disease is now consistent with the significance of Sirt 1 and the immune response. Global chronic illness may be reversed by combining dietary interventions with lifestyle changes. Diets low in calories that increase Sirt 1 have been shown to support anti-aging gene therapy, miRNA function, transcriptional factor control, and interactive nuclear receptor signaling in a variety of cells and tissues. These processes are relevant to immune response maintenance and the prevention of autoimmune disease, which may be linked to the development of MODS and chronic diseases worldwide (78). In microglial cells, SIRT1 activation also reduced the expression of the protein inhibitor of activated Stat 1 and K379 acetyl-p53. Furthermore, it significantly increased

microglia's M2 polarization, which changed their capacity to phagocyte and increased cell motility. Treatment with minocycline reduced neuroinflammatory responses and enhanced microglia M2 polarization. SIRT1 plays a role in preserving the homeostasis of microglial polarization, and minocycline regulates the activation of SIRT1. Consequently, the findings suggest that SIRT1 activation could be a valuable therapeutic target for the management of illnesses linked to neuroinflammation. In the pathophysiology of mood and cognitive dysfunction, microglial activation and the expression of inflammatory mediators, such as chemokines and cytokines, in the brain are thought to be important events. Microglia undergo morphological changes to resemble larger ameboid cells upon stimulation. They can then become polarized into an inflammatory or anti-inflammatory phenotype in response to pro- or anti-inflammatory microenvironments; these microglia are known as M1- or M2-activated microglia, respectively. Inducible nitric oxide (NO) synthase (iNOS), cyclooxygenase 2 (COX-2), proinflammatory cytokines, and increased secretions of neurotoxic factors are examples of proinflammatory mediators that are produced by activated M1-polarized microglia. This inflammation in the brain may result in neuronal degeneration. On the other hand, M2-polarized microglia that have been activated can secrete neurotrophic factors to suppress inflammation, promote the production of anti-inflammatory mediators like IL-4, IL-13, arginase 1 (ARG1), and chitinase-like-3 (Ym-1), and promote cell migration and phagocytic activity to remove debris. The creation of substances that can alter the shift of M1/M2 phenotypes has been proposed as a practical treatment approach for mental and neurological conditions that involve inflammation. Moreover, aging-related cognitive decline and neurodegeneration are facilitated by microglia lacking SIRT1. Numerous transcriptional factors, including nuclear factor κB, p53, and forkhead box O 1, have been reported to be modified by SIRT1. Alzheimer disease (AD) patients' brains have been shown to have both neurons and microglia with upregulated expression of p53, which is linked to tau phosphorylation. Furthermore, it has been shown that elevated transcription-dependent p53 activity in microglia is linked to inflammatory cytokine release and neuronal synaptic degeneration. All things considered, diseases linked to microglial neuroinflammation may benefit from targeting SIRT1. The findings imply that SIRT1 activation successfully reduces microglial cells' neuroinflammatory reactions. According to research, p53 deacetylation in microglial cells may be the mechanism through which lipopolysaccharide (LPS) or peptidoglycan (PGN)-induced inflammatory responses are inhibited when SIRT1 is activated. Furthermore, HO-1 expression is induced by SIRT1 activation, which also promotes the transition of a microglial phenotype toward M2 polarization. Furthermore, administration of the microglial activation inhibitor minocycline partially inhibits microglial activation by activating SIRT1. According to findings, minocycline also lowered the amounts of acetyl-p53 and iNOS in the brain tissue of an inflammatory mouse model. The current study's findings corroborate earlier findings that SIRT1 activation in microglial cells dramatically suppresses p53 acetylation and the production of proinflammatory cytokines like iNOS and IL-1β. Parkinson's disease (PD) and Alzheimer's disease (AD) are two neurodegenerative illnesses that are linked to p53 expression. Furthermore, p53 expression has been found to be elevated in the brains of AD patients' microglial cells, although a p53 knockout mouse model of AD showed decreased tau phosphorylation. Additionally, exposure to β-amyloid reduced the neurotoxicity that microglia triggered by blocking p53-mediated pathways (79).

depletion of microglia

Researchers have created microglia depletion methods utilizing pharmacological or genetics in response to the premise that microglia activation worsens AD progression. Depletion of microglia in AD mice models has been demonstrated to produce positive outcomes. It is well known that CSF1R is an

essential surface receptor for microglia (16) as cited in Si et al., 2023). In many AD mouse models, CSF1R inhibitors can reduce the development of neuritic plaques, dendritic spine loss, and neuroinflammation while also enhancing cognition (12) Sosna et al., 2018 as cited in Si et al., 2023).

Human NSC in betterment of AD

Studies using rodent AD models have demonstrated that human NSCs (hNSCs) from the embryonic telomere can move and develop into neurons and glial cells in the lateral ventricle of mice with AD. This phenomenon diminishes glial and astrocyte hyperplasia, tau phosphorylation, and A-42 levels (32). enhances neuronal, synaptic, and nerve fiber density and promotes the creation of endogenous synapse (37). Neurotrophic elements It has been demonstrated that NSCs' secretions enhance memory performance, and that NSCs that overexpress the -degrading enzyme decrease the aggregation of A β (Tang et al., 2008; Wu et al., 2016; (40) as cited in Si & Wang, 2021). A β and tau protein levels were unaltered following the transplantation of human-derived NSCs into 3xTg mice, but memory performance and synaptic density improved, showing that the transplantation of human-derived NSCs may only correct symptoms ((9),(1) as cited in Si & Wang, 2021).

Induced Pluripotent Cells

In a five familial AD (5 FAD) transgenic mice model, human iPSC-derived macrophage-like cells were genetically altered to produce the A-degrading protease neprilysin-2, develop into functional neurons, and lower A levels therapeutically (Takamatsu et al., 2014 as cited in (37).

The transition from the pro-inflammatory cytokine response to the anti-inflammatory cytokine response through neurotrophin-related reprogramming effects could also explain the significant improvement in neural function following the injection of human iPSC-derived NSCs into the hippocampus of a mouse model of stroke ((17) as cited in (37).

Current trials

microglia's impact on current research

Many studies have confirmed that microglia promote the development and progression of neuroinflamation (46); (5) as cited by (34).

So, it has become well established that microglia play a crucial role in AD progression. The microglial lysosome has been identified as the principal intracellular environment that promotes the proliferation and aggregation of Aβ plaques (Spangenberg et al., 2019 as cited in Zhang et al., 2021). This was confirmed once again in this study when Aβ aggregation was observed in transgenic mice. The observation was done at the time of plaque formation in 15-month-old mice, the results showed intracellular aggregates that had the appearance of small plaques, inta-lysosomal plaques within microglia as well as ramified microglia. However, there was an absence of nearby plaques outside the microglial environment, strongly suggesting that the microglia were the source of the observed plaques.

Inhibitors

From this knowledge it can then be extrapolated that depletion of microglia can halt the progression of plaque formation in AD. Colony stimulating factor 1 (CSF1) is a crucial element in the survival and development of microglia; thus, continued administration of CSF1R inhibitors is proving to be an effective, non-invasive approach to precisely ablate the microglia, and has been adopted in numerous studies. In 2018, Sosana and colleagues gave 3 months of treatment to 2-month-old mice, with a selective colony stimulation factor 1 receptor (CSF1R) inhibitor, PLX3397. The mice selected exhibited

comparable levels of the human APP and PS1. After 3 months, it was found that early long-term administration of PLX3397, resulted in a dramatic decrease of intraneuronal amyloid as well as neurotic plaque deposition. Reductions were also seen in soluble fibrillar amyloid oligomers in brain lysates, a depletion of soluble

pre-fibrillar oligomers in plasma. On fear conditioning tests done during behavioral analysis, there was improvement in cognitive function (Sosna et al., 2018 as cited by Zhang et al., 2021).

Another CSF1R inhibitor, JNJ-40346527 currently being developed by Janssen Biotech in partnership with the University of oxford is currently in phase 1 of clinical trials (4). This mechanism of microglia suppression through CSF1 reduction is also potentially achievable through genetic modification. Downregulation of CSF1 production was observed by in vitro deletion of a CSF1 enhancer in mouse embryonic stem cells mediated by the CRISPR/Cas9 system (53) as cited by Zhang et al., 2021).

Drugs enhancing microglia's role

The general intravenous anesthetic propofol, has also recently been seen to have some neuroprotective effects through microglia suppression. A recent study done by researchers affiliated with Tongi University in China, investigated this connection and their results suggested that administration of propofol in transgenic mice subsequently hindered the activation of microglia especially through the PI3k/Akt pathway. The drug seemed to have this regulatory effect through microRNA, especially miR-106b, which was identified as the vital miRNA that mediates the anti-inflammatory effects that propofol has on microglia (36).

Antibodies approach

Emerging research shows microglia to play a role also in the promotion of tissue repair (34).

Another approach that is proving to be effective in the management of neurodegenerative diseases like AD is through the replenishment of healthy microglia. Cells that closely resemble microglia have been successfully derived from induced pluripotent stem (iPS) cells (14). These cells perform phagocytosis similarly and respond to the similar negative stimuli as Human primary microglia. The TREM2 protein, which is expressed by microglia, as well as other phagocytic cells such as, osteoclasts, dendritic cells, and macrophages, is thought to be important in the proper functioning of microglia phagocytosis. Mutation in this protein has been linked to the development of progressive dementias, such as Nasu-Hakola disease (NHD), frontotemporal dementia (FTD) and AD, due to defective phagocytosis. The TREM2 transgenic mice showed enhanced learning as well as improvements in memory deficits (28).

Targeting Microglial Immunoreceptors

Due to the fact that it has been established that TREM2 mutation increases the risk for AD (28) and its deficiency in an AD patient aggravates the symptoms by reduction of Aβ phagocytosis and clearance (Wang et al., 2015), it can then be deduced that enhancement of TREM2 activity has a positive effect on the symptoms of AD. Large pharmaceutical companies have recently become heavily interested in this area of research. Alector and Denali Therapeutics are two California- based companies showing promising results in the development of their TREM-2 agonist drugs, with Denali, in partnership with Takeda Pharmaceutical Company, already venturing into early human studies (4). Certain individual antibodies have been identified that exhibit agonistic effects on TREM2. These antibodies currently being investigated are antibody 1, antibody 2 (10), AL002c (Wang et al., 2020), and AL002a (51). Another monoclonal antibody of note, VGL101 is currently being developed by Virgil Neuroscience.

The company recently received approval from the Australian Human Research Ethics Committee and is currently undergoing phase 1 human trials on healthy volunteers receiving single and multiple doses. However, in the United States, where the company is based, they have recently entered phase 2 of their clinical trial, Where the first dose of the novel drug was given to a patient with ALSP.

Another antibody that has been recently found to be effective in the enhancement of TREM2 activity is antibody 4D9 (Schlepckow et al., 2020). Its mechanism of action is thought to be through reduction in proteolysis of TREM2, thereby exerting protective effects in AD.

The second major microglial receptor is CD33. Polymorphisms in the CD33 gene are thought to be involved in the suppression of Aβ phagocytosis, leading to the plaque accumulation mediated pathologies seen in AD (Zhao, 2019 as cited by Zhang et al., 2021). Inhibition of CD33 is thought to be a promising method for resistance to the neurotoxic effects of CD33 in the progression of AD. CD 33 was identified in a study as one of the strongest potential candidates for the development of anti-AD therapies (Zhang et al., 2016), due to the existence of numerous available CD33 inhibitory antibodies that could also be effective as anti-AD therapies. In particular, the drug lintuzumab, which is presently used as a treatment for acute myelogenous leukemia, may be a viable candidate for treating AD. Novel drugs that inhibit CD33 are also being developed as potential therapies. AL003, a CD33 inhibitor was being developed by Alector, along with other AD therapies in their pipeline, however the trial for this drug was put on hold after phase1.

P22 a sialic acid-based ligand P22 exhibits high specificity for human CD33, was developed in a study by Parker and colleagues. The ligand works by binding to CD33 to then mediate an increase in Aβ phagocytosis by microglia (41) as cited by Zhang et al., 2021).

Gene targeted therapy

MS4A is a gene that encodes a transmembrane protein which is expressed selectively in microglia in the brain and is associated with control of microglia functionality and potential viability. It is involved in the regulation of TREM2 and has been identified as a major indicator for AD risk (13). A novel drug, AL044 is currently in phase 1 of clinical trials, targets this gene. Pre-clinical studies of this drug have shown it to be involved in the control of key microglial signaling systems such as proliferation, lysosomal activity, migration, phagocytosis, and immune response. AL044 is thought to recruit microglia to counteract multiple Alzheimer's pathologies (20).

Prospects and conclusions.

Some new prospects in stem cell research

We must use a dynamic approach while examining AD's etiology. The latent stage of AD is very long before clinical manifestation. The prodromal phase, which lasts for a long time, is most receptive to treatment. Early intervention may be able to stop neuronal degeneration and turn AD's clinical course around. As a result, we should put more effort into discovering new and cutting-edge markers for this asymptomatic stage of AD. As an illustration, disease-specific exosomes, microRNAs, blood or CSF early disease indicators (particularly early biomarkers for neurodegeneration), paired with enhanced amyloid beta and tau imaging technologies, which offer superior AD predictive values ((21); (45); (23); (42) as cited in (25). The emergence of new stem cell-based technologies and associated goods will fundamentally alter this industry int he near future. For instance, genetic editing of stem cells can enhance their immune-modulatory and neurotrophic activities (15) as cited in (25). On the other hand,

more meticulously planned AD clinical trials that focus on more people in the prodromal or preliminary stages of the illness should produce better outcomes soon (25). Also, to beta amyloid or tau pathology, new models should consider characteristics of multi-neurotransmitter loss, disease progression, and late illness onset. These models would ideally exhibit neuronal loss, synaptic breakdown, and vascular pathology like Alzheimer's disease. Future research should incorporate disease modifiers such systemic inflammation, insulin resistance brain injury dietary conditions inactivity and obesity. Recognizing the unique roles that microglia, macrophages, astrocytes, neurons, and endothelial cells play in causing neuroinflammation, this will reveal which inflammatory processes—at various stages of Alzheimer's disease-are beneficial, harmful, and irrelevant for disease pathogenesis. We should utilize the impact of immune function, epigenetic, and microbiome mutations on neuroinflammation in Alzheimer's disease.

Recent findings, such as SNPs in immune-associated genes, epigenetic immune regulation, and the impact of the microbiome on innate immunity, indicate a direct immune-related modification of a onset, progression, and phenotype of Alzheimer's disease. These findings should be taken into consideration (24).

Impact of microbiome on innate immunity and bacterial lipopolysaccharides induce neuroinflammation in microglia.

In 60–70% of dementia cases, Alzheimer's disease (AD) is the most prevalent type of dementia. Concern has grown over the role that the gut microbiota plays in host metabolic regulation, which serves as a link between dietary lipids and the health of people with AD. The composition of the microbiome is important for the gut-brain axis and has been connected to neurodegenerative diseases. Short-chain fatty acids, like butyric acid, which have a significant impact on the gut-brain axis and affect brain amyloid beta levels and plaque deposition, may be released by microbiological fermentation. Histone acetylation in the brain is influenced by butyric acid, and deacetylation is crucial for metabolic control, brain amyloidosis, and the aetiology of AD. The relevance of gut dysbiosis may be the reason for the induction of the pathogenesis of AD, and numerous mechanistic investigations are necessary to ascertain the underlying mechanisms for safe and effective probiotic treatment for AD. Gram negative bacterial contamination is linked to the production of toxic lipopolysaccharides (LPS) structures that raise cholesterol, induce inflammation, and aggregate amyloid beta, all of which are linked to neurodegeneration. Probiotics have been shown in several studies to have positive effects on slowing the progression of Alzheimer's disease. Because gut microbiota and AD are closely related, probiotics have recently been proposed as possible therapeutic options for AD.

A probiotic is a live microorganism that, when given in sufficient quantities, benefits the host's health. In order to correct intestinal microflora and dysbiosis, the presence of gram positive and gram negative bacteria in probiotic products, such as dairy products (yogurt, cheese, etc.), is currently a major area of research interest. Gut dysbiosis-released inflammatory metabolites and cytokines have an impact on both brain size and the blood-brain barrier (BBB). Increased BBB permeability may make it simpler for immune cells or mediators to enter the brain, speeding up neuroinflammation. BBB permeability is regulated by innate immune cells, such as mast cells and microglia, and is sensitive to pro-inflammatory mediators.

The central nervous system (CNS), autonomic nervous system (ANS), hypothalamic pituitary adrenal axis (HPA), and enteric nervous system (ENS) all provide a two-way communication link between the gut and the brain. additional research The effects of aging-related changes in the gut microbiota's composition are linked to an increase in Enterobacteriaceae and other Gram-negative bacteria. Age-

related decreases in the levels of SCFAs (acetate, butyrate, and propionate) in the intestine have been linked to the release of lipophilic acid stress (LPS) from these Gram-negative bacteria.

Studies indicate that bacterial endotoxins could potentially be linked to amyloidosis and Alzheimer's disease through the accumulation of amyloid beta. Long-term administration of bacterial LPS, a component of Gram-negative bacteria's outer cell wall, imitates many of the inflammatory and degenerative brain traits seen in Alzheimer's disease patients. The ability of amyloid-peptide (Aβ) to aggregate into fibrils, which are the main component of amyloid plaques, is one of the traits of AD and LPS-containing E. coli. One of the features of AD is undoubtedly the ability of amyloid-peptide (Aβ) to form fibrils among brain cells, and extracellular amyloid can be formed by LPS-containing E. coli bacteria. The evidence suggests that extracellular amyloid can be synthesized by Gram-negative E. Coli bacteria.

By attaching itself to the TLR4/CD14 complex on brain microglia or peripheral monocytes/ macrophages, LPS triggers NF-B and increases the synthesis of cytokines such as TNF, IL1, and IL-6. Additionally, LPS disrupts LDL receptor related protein (LRP), which is required for the elimination of Aβ from the brain, and has negative effects on the blood-brain barrier. The interactions between the gut, brain, and microbiota may lead to aberrant lipid metabolism in the liver and hypercholesterolemia, which may hasten AD. Toxic lipids and LPS have been linked to accelerated brain amyloidosis and an increased risk of AD. Beneficial probiotics may enhance lipid metabolism and reverse hypercholesterolemia, which is linked to Alzheimer's disease and amyloidosis (80). The most frequently used stimulus to study microglial reactivity and pro-inflammatory responses, lipopolysaccharide (LPS), really results in a mixed inflammatory response. When IFNγ+TNFα was used, this mixed profile was less noticeable, and the stimulus was more obviously pro-inflammatory. Microglia have been shown to exhibit mixed profiles in vivo, exhibiting increases in pro- and anti-inflammatory molecules. This has been observed in traumatic brain injury models in rodents. The investigation examines how microglia react to different stimuli in terms of inflammation, with a particular emphasis on contrasting the actions of lipopolysaccharide (LPS) with those of IFNγ and TNFα combined (IFNγ+TNFα). LPS, which is a byproduct of the E. Coli bacteria, uses TLR4 to activate inflammatory signaling pathways; endogenous TLR4 ligands released subsequent to injury can also cause inflammation. The decision to compare LPS with IFNγ+TNFα was prompted by the higher TNFα and IFNγ levels linked to CNS damage, which may trigger detrimental responses in microglia. The study also looks at the possibility of plasticity in microglial reactive states, an area that is still not well understood (81).

Some limitations

Although the safety of MSCs has been shown through clinical testing, efficacy hasn't been established. It is important to remember that when AD is clinically diagnosed, neuronal loss and abnormal proteins have accumulated in numerous brain regions, making it challenging to stop the progression of the illness. Additionally, in several clinical trial protocols, participants only receive stem cell infusions a few times, even though they may require several stem cell infusions over a lengthy period. Autologous MSCs were employed in several studies (such as those that used MSCs generated from adipose tissue). Autologous MSCs may experience senescence due to the elderly age of AD patients, which impairs their capacity for regeneration. Most clinical trials for AD were intravenous the lungs and spleen will hold the majority of intravenously delivered stem cells (47) as cited in (25). The varied mechanism off various stem cells have been disclosed by several preclinical investigations, which also showed the immense potential of stem cells to cure AD. The main issue with this line of study, though, is how

challenging it is to convert animal experiments into human trials. In fact, scientists have successfully treated AD in transgenic mouse models using close to 100 different techniques. Unfortunately, virtually every strategy has either never been tested on humans or has failed in human clinical trials. Clearly human therapeutic outcomes cannot be predicted using rat models and associated pathogenic presumptions. As a result, the development of more precise models is required for AD cell treatment. More studies on cell treatment are required now that the objective of accurately imitating the degenerative progression of AD in the human body has been accomplished (26).

Possible diagnostic clues

With relation to different biomarker tests that involve proteomics, lipidomics, and genomics that help with drug therapy to prevent programmed cell death with relevance to severity of global chronic disease progression, critical interpretations and analysis in diagnostic proteomics have accelerated. y. Anti-aging gene Sirtuin 1 (Sirt 1) analysis is now necessary for therapeutic drug effectiveness and the measurement of multiple proteins/peptides for patient care requirements. Sirt 1 is related to toxic amyloid beta:protein interactions and is relevant to therapeutic drug metabolism in diabetes and neurodegenerative diseases. The methodical study of numerous proteins to determine their structure, functionality, and ability to regulate biological systems in both health and disease is known as proteomics. Peptide/protein complex analysis has seen a rapid advancement in mass accuracy and sensitivity in methods and technologies. Research in proteomics with proteomic pattern diagnostics is currently growing. These days, the plasma proteome plays a critical role in interpreting the relationship between the severity of the global progression of chronic disease and the prevention of programmed cell death. Proteomic-based methods for biomarker research may make it possible to clarify pathways and identify people who are most likely to react favorably to particular pharmacological therapeutic interventions.

The analysis of the plasma proteome, which may be relevant to neuron mitochondrial apoptosis, has accelerated the field of diagnostic proteomics and its relevance to early diagnosis of neuron apoptosis. Sirt 1 is now linked to drug metabolism, mitochondrial apoptosis, and neurodegenerative diseases. It also plays a significant role in mitochondrial biogenesis and the regulation of protein/amyloid beta.

Toxic amyloid beta-protein interactions regulated by Sirt 1 are essential for drug metabolism with reduced plasma Elevated drug-protein or drug-xenobiotic interactions are correlated with elevated Sirt 1 levels.

With relation to different biomarker tests that involve proteomics, lipidomics, and genomics that help with drug therapy to prevent programmed cell death and with relevance to the severity of chronic disease progression worldwide, critical interpretations and analysis in diagnostic proteomics have accelerated.

With relation to different biomarker tests that involve proteomics, lipidomics, and genomics that help with drug therapy to prevent programmed cell death and with relevance to the severity of chronic disease progression worldwide, critical interpretations and analysis in diagnostic proteomics have accelerated. In chronic diseases associated with bacterial lipopolysaccharides (LPS) and patulin that are related to faulty posttranslational/post transcriptional alterations, dietary regulation of Sirt 1 is important. Although the translational application of proteomic technologies has made progress and faced challenges in interpreting post-translational modifications and protein-protein interactions in disease, mycotoxin and lipopolysaccharide (LPS) have gained importance and have the potential to override proteomic interpretations in both health and disease. Because amyloid beta-acute phase protein

interactions with LPS are essential for hepatic Sirt 1 repression and membrane transformation with implications for drug metabolism, there is growing interest in plasma Sirt 1 analysis. Sirt 1 is now known to be an inflammatory target protein in vivo because LPS controls its levels. By interfering with apolipoprotein E-phospholipid transfer protein, apolipoprotein A1, albumin, transferrin, and lactoferrin, LPS inhibits toxic amyloid beta metabolism. Protein interactions and toxic amyloid beta interact with Sirt 1 repression to control biological systems in health and disease. This inactivation of drug/xenobiotic metabolism accelerates the progression of chronic diseases. Early plasma Sirt 1 analysis is necessary for the identification of disease protein biomarkers linked to the inactivation of toxic amyloid beta and therapeutic drug metabolism, which is important when applying proteomics to the progression of disease (82).

In human and mouse astrocytes, LPS activates the toll-like receptor 4 (TLR-4), which has been connected to neuroinflammation and neuronal death. By attaching to cell membranes that encourage amyloid beta (Aβ) aggregation and fibril formation, LPS-related toxicity may have an impact on the cholesterol in neuron membranes and cause accelerated neuron death. LPS are endotoxins that are vital parts of gram-negative bacteria's outer membrane. They are made up of segments that are covalently linked, a surface polymer of carbohydrates, a core oligosaccharide, and an acylated glycolipid that can bind to cell membranes and change the way that membranes interact, LPS controls a number of other acute phase proteins (APP) involved in Aβ aggregation, including transferrin, albumin, phospholipid transfer protein, LPS binding protein (LBP), and albumin, as well as plasma acute phase proteins (gelsolin, serum amyloid protein A, serum amyloid protein, C-reactive protein, clusterin, and transthyretin).

The LPS receptor, also known as the cluster of differentiation 14 (CD14) receptor, is involved in the metabolism of Aβ in the brain. The CD14 receptor aids in the microglia's coordination, which facilitates oxidative and Aβ-mediated neuronal death.

Increased plasma LPS levels in developing nations have given rise to serious concerns regarding CD14 regulation of TLR-4-mediated accelerated neuronal death. present evidence that LPS suppresses the nuclear receptor Sirtuin 1 (Sirt 1), potentially having harmful consequences by interfering with Sirt 1's function in transcription factor regulation. The role of Sirt 1 in the death of neurons has now been linked to cellular proteins that are associated with Aβ aggregation and accelerated neuron death, such as tau, alpha-synuclein, cellular prion protein (PrPc), and heat shock protein (HSP). Sirt 1 is repressed by LPS, and HSP regulates PrPc and Aβ aggregation, which are important for mitochondrial apoptosis and neuronal death. Magnesium deficiency is associated with LPS and its role in protein aggregation with the induction of mitochondrial apoptosis linked to stroke caused by epilepsy.

It is important to closely monitor other Sirt 1 inhibitors, such as alcohol, fructose, palmitic acid, suramin, and sirtinol, to avoid mitochondrial apoptosis and neuronal death. To stop Sirt 1 downregulation, excessive intake of arginine, patulin, xenobiotics, and butyric acid should be avoided (82).

Conclusion

Microglia’s involvement in neuroinflammation is key in Alzheimer’s, both concepts need to be studied in much more detail and on different models as well as tested with microglia’s receptors, by either uptake or downregulating them or by pruning microglial antibodies, these three approaches seem to be effective in mice models to a certain degree, hence more data should be retrieved with different factors

affecting the mice models, as to get a better understanding as of how different bodies with different physiologies react to antibodies. Sirt 1 aswell as environmental dietary factors which help which plays a key role in neuron homeostasis. regulating LPS absorption are crucial for preventing neurodegeneration. LPS may accelerate appetite dysregulation and chronic diseases by suppressing anti-aging genes.

Sirt1 activation reduces neuroinflammatory responses and enhances microglia M2 polarization, which may have therapeutic implications for diseases associated with neuroinflammation. Sirt1 activation suppresses p53-mediated pathways, potentially reducing neurotoxicity. In summary, the intricate interplay between various molecular pathways, gene regulation, and environmental factors in the context of neurodegenerative diseases, offers potential therapeutic targets for intervention.

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