The Potential Role of Cytokines and growth factors in the pathogenesis of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a neurodegenerative disorder characterized mainly by the gradual decay in neuronal function as a consequence of diverse degenerating events primarily including mitochondria dysfunction and cascades of neuro-immune reactions. Besides the acquired harmful reactive oxygen species (ROS), neurotoxins, and amyloid-beta (Aβ) and TAU pathologies in neurons, accumulating evidence with time underlined the roles of cytokines and growth factors in the AD pathogenesis. It may help us in evaluating the propensities and specific mechanism(s) of cytokines and factors impacting neuron upon apoptotic decline. Proinflammatory cytokines often induce inflammation in AD and AD-like pathogenesis in response to the apoptotic scenarios where some growth factors are involved in cytokinetic reactions to activate microglia and causing inflammation in AD. In this report, we comprehensively reviewed role of cytokines and chemokines in immune response to AD and neuropsychiatry. We provided insights into the neuroinflammation and the role of diverse factors including the pro-/anti-inflammatory cytokines, APP, TAU phosphorylation, glycation end products, complement system and the role of glial cells. Also, we discussed the pathogenic and protective role of macrophage migration inhibitory factors, choroid plexus-, neurotrophic- and hematopoietic -related growth factors in AD. We further shed light on the availability and accessibility of the cytokines across the blood-brain barrier in the AD pathophysiology. Taken together, emerging role of these factors in AD pathology emphasized the importance of building novel strategies for an effective therapeutic/neuropsychiatric management of AD in clinics.

Keywords: Alzheimer's disease; cytokines; chemokines; neuroinflammation; neurotrophic factors; pathophysiology; Blood brain barrier; mild cognitive impairment; brain health; therapeutics

 doi:10.20944/preprints202108.0237.v1

Abbreviations: AD: Alzheimer's disease; BBB: Blood brain barrier; MCI: mild cognitive impairment; ROS: reactive oxygen species, CNS: central nervous system

Highlights:

1. Cytokines and growth factors play crucial roles in the AD pathogenesis.
2. Macrophage migration inhibitory factors, choroid plexus-, neurotrophic- and hematopoietic -related growth factors have intrinsic functions in the AD pathogenesis.
3. Cytokines and growth factors impact the molecular processes in neurons necessary for homeostasis in cognitive mechanisms.

1. Introduction

Neurodegeneration has been a puzzle gradually elucidating with the progress of ample research and the investigation on dementia and progressive cognitive decline. Dementia is understood as the decline in memory and other fundamental cognitive functions. One such disease of focus is Alzheimer's disease (AD). AD is the most occurring neurodegenerative disease of the world characterized chiefly by the gradual death of neurons consequential of degenerating mitochondria that decay in a cascade of neuro-immune reactions [1]. The accumulation of harmful reactive oxygen species (ROS), neurotoxins, and TAU pathologies that result in neurofibrillary tangles consisting of TAU protein and including amyloid-beta (Aβ) which eventually form plaques after accumulation from the aberrant processing of its precursor protein; amyloid precursor protein (APP).

Cytokines are non-structural proteins within the molecular weight range of 8000-40,000 Da. In general, they can be described as inflammatory peptides aiding the immune defense response of the body. Almost all nucleated cells are capable of synthesizing them. These cells, in turn, can respond to cytokines too. Though cytokines cannot be tagged with a particular amino acid sequence motif, they can be grouped into certain classes based on their

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biological activities. The vast spread of biological activity of cytokines ranges from cell proliferation to apoptosis, from cell differentiation to inflammatory responses. Cytokines are also termed lymphokines since they are primarily involved in the differentiation of different types of T lymphocytes *viz.* T helper cells and T regulatory cells from undifferentiated cells [2]. Many of these proteins e.g. interleukins (ILs), interferons (INFs), tumor necrosis factors (TNFs), and certain growth factors are produced by neurons and glial cells of the brain. Levels of IL-1α, IL-1β, IL-6, TNF-α, IFN-α, macrophage colony-stimulating factors, IFN-α and IL-8 receptor type B are enhanced in blood and cerebrospinal fluid (CSF) in AD patients. Nerve growth factors (NGF), growth-promoting properties of APP, vascular endothelial growth factor (VEGF) play vital roles in the pathophysiology of AD. Growth factors, proteins by nature support the survival of cells within the nervous system. They are vital players for the proper development of the brain. In the central and peripheral nervous systems, they stimulate axonal growth and regulate the growth of different kinds of cells.

AD is named after German psychiatrist and neurologist Alois Alzheimer [3]. In 1906, the doctor noted some peculiar findings in the brain of a patient who expired after suffering from memory loss, disorientation, paranoia, and unpredictable behaviors. AD causes a gradual decline in cognitive processes (Table 1). AD, by nature, is an insidious, progressive, degenerative disorder. With the improvements in medical science, life expectancy has increased a lot. Hence, the occurrence of degenerative disorders like AD is also increasing with the increase in the geriatric population. AD invariably starts from the hippocampus (responsible for new memory generation) making anterograde amnesia a primary symptom of the disease. As neurofibrillary tangles start to spread outward towards the frontal lobe, dementia is followed by speech problems, mood imbalance, inability in decision making progressively [4]. Genes like senilins, SORL1, APP, and ApoE4 are involved in the onset and development of AD [4]. Early onset AD is generally familial while late onset AD is largely

 doi:10.20944/preprints202108.0237.v1

related to SORL1. From the viewpoint of pathophysiology, AD is characterized by intracellular neurofibrillary tangles and extracellular senile plaques.

To identify and elucidate the role of cytokines and their co-associating factors, such as growth factors, in the immune system and in response to the pathogenesis of AD, is key understanding to increase the potentials for therapeutic intervention. Current review aims to analyze research data, prior AD-related research, and affiliations between connected fates of inflammatory and immune responses of AD, to help identify the role of cytokines and key growth factors implicated in AD.

2. Immune response in AD: role of cytokines

It is now understood that Aβ and TAU pathologies are the main driving factors in the escalation of neurodegeneration and progression of AD. The role of the immune system in central nervous system (CNS) pathologies such as cell-mediated immunity in the reaction of neurons to the accumulation of Aβ plaques and TAU neurofibrillary tangles are innate in nature. In the initiating events of neurodegeneration, the immune reactions which trigger macrophages, M2 and sometimes M1 are activated [5]. These macrophages secrete chemical messengers in interneuronal communications and develop autoimmune neurotoxicity including those reactions that lead to neuroinflammation and escalation of AD. The immune system employs chemical messengers known as cytokines, which play a major role in immune responses following the activation of microglia in the pathology of AD. These messengers determine the mechanisms and reactions that take place in the immune system in response to abnormal changes in the neurons triggering the recruitment of other defensive cells including neutrophils and macrophage progenitor cells already circulating in the blood post-hematopoiesis and through blood-brain barrier (BBB).

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In the case of AD, β amyloids originating from APP trigger the rest of the pathologies. β amyloids outside the neurons and neurofibrillary tangles inside the neurons make up for the development of AD [6,7]. β amyloids, in turn, produce immune response activating complement systems. In CNS, the immune system is programmed to functionally respond to pathological changes such as those presented by the progression of AD [5]. The immune system activation observed in AD is labelled as neuroinflammation [8]. Misfolded and aggregated proteins i.e. β amyloids act through danger-associated molecular pathways (DAMP) to bind pathogen recognition receptors like CD14, CD36, CD36, α6β1, integrin, and toll-like receptors [9]. These, in turn, control functions of ROS, NO, IL-1β and TNF-α. It has been shown experimentally that, contrary to antiquated conclusions about neuroinflammation being a mere pathological advent in the late onset of this dementia-related disease, neuroinflammation observed as expressed in mild cognitive impairment (MCI), early-onset and late onset AD are initiating events predominantly driven by the CNS resident immune cells, such as microglia and perivascular myeloid cells [8]. Genetic variants and transcription factors also determine the expression of activated microglia in the pathological environment. Damaging or degenerating neurons give off signals acting as a form of microglial control switch that stimulates microglia which could become cytotoxic from the reactive intermediates solicited such as pro-inflammatory cytokines [10]. Cytokines may act in an autocrine, paracrine or endocrine fashion. In response to a change in homeostasis, microglia must first be activated, changing it from a static to a primed state. Changes in infiltrating monocytes that support CNS immune response in the parenchyma and neuronal progenitor granule crossing of the BBB might be a hallmark for early detection of AD and propensity of inflammatory response and neurodegeneration [11]. Asymmetrical changes in serum and plasma levels of cytokines may indicate changes in early cytokine levels widely reported in

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macrophage precursor cells that may confer a greater risk of developing neurodegeneration and abnormal macrophage morphology.

3. Role of cytokines and chemokines in neuropsychiatry

The study of cytokines to understand the pathophysiology of neuropsychiatric disorders like dementia, anxiety, delirium has been pioneered by Dr. M. Maes who first linked the vegetative symptoms with enhanced presence of IL-1, IL-6 and haptoglobin [12]. Chemokines regulate the migration of microglia and the recruitment of astrocytes to sites of inflammation. Chemokines are upregulated at sites of Aβ plaques. Aβ mediated cell mediators such as monocytes also are responsible for the generation of IL-8, monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1α and macrophage inflammatory protein (MIP) 1β. Lipopolysaccharide stimulated astrocytes to secrete cytokines including IL-6 and TNF-α, activated astrocytoma cells secrete IL-6 and IL-8 and monocytes secrete IL-8 under the influence of Aβ peptides [13]. Synergistic activity of cytokines has also been reported along with Aβ peptides e.g. TFN-γ synergizes with Aβ to enhance secretion of TFN-α and reactive nitrogen species [14]. IL-1β displays proinflammatory actions via MEK 1/2, JNK-activated α-secretase cleavage and upregulated ADAM17/TACE pathway to increase sAPPα secretion [15]. On the contrary, IL-1β can also serve as an anti-amyloidogenic factor by decreasing sAPPβ and amyloidogenic Aβ fragment levels by reducing β-secretase cleavage [16]. It was also suggested that increased Aβ clearance by microglia in models of sustained IL-1β neuroinflammation could involve Th2 cytokines, such as IL-4 [17]. A feedback signalling loop between Aβ and IL-1β was proposed in which Aβ can induce the production of IL-1β [18]. Migration of astrocytes to amyloid plaques is promoted by chemokines CCL2 and CCL3, which are released by activated microglial cells.

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Important pathways involved in the pathogenesis of AD include amyloid cascade hypothesis, TAU hypothesis, cholinergic hypothesis and excitotoxicity hypothesis. In the case of AD, CSF dysfunction is noticed even before cognitive decline. Activities of mTOR cause vascular irregularities in the brain decreasing cerebral blood flow which in turn sets up cognitive decline. Amyloid cascade hypothesis identifies accumulation of Aβ plaques at different areas of CNS and related changes as the principal factor behind the development of AD [19]. TAU hypothesis suggests hyperphosphorylation of TAU leading to neurofibrillary tangles instead of supporting axonal microtubules is instrumental in case of neurodegenerative disorders [20]. Cholinergic hypothesis focuses on symptoms of cognitive decline and presents malfunctioning of cholinergic neurons as a pathophysiological factor towards initiation of AD [21]. Excitotoxicity refers to the unprecedented death of nerve cells due to overstimulation of certain amino acid receptors [22]. A high concentration of glutamates activates N-methyl-d-aspartate and α-amino-3-hydroxy-5-methylisoxazole propionic acid receptors. As a result, voltage gated calcium allows the entry of extracellular calcium into cells. Hindrance in neuronal energy metabolism leads to cell death.

4. Neuroinflammation

Inflammation is the response of our body system to eliminate both sources of cell injury along with the cell and tissue debris originating from the insult. The immune system activation observed in AD is labelled as neuroinflammation. Though classical signs of inflammation like swelling, heat and pain are absent in brain inflammation, it characteristically involves increased monocytes and glial macrophage cells [23]. In the initiating events of neurodegeneration, the immune reactions which are involved that trigger macrophages, M2 and sometimes M1 are activated [24]. These macrophages secrete chemical messengers in interneuronal communications and develop autoimmune neurotoxicity including those reactions that lead to neuroinflammation and the escalation of AD. Activated

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cells strongly produce inflammatory mediators such as proinflammatory cytokines, chemokines, macrophage inflammatory proteins, monocyte chemo-attractant proteins, prostaglandins, leukotrienes, thromboxanes, coagulation factors, ROS (and other radicals), nitric oxide, complement factors, proteases, protease inhibitors, pentraxins and C-reactive protein. Upregulated immunoinflammatory events play important roles in the pathogenesis of AD.

Chronic neuroinflammation (immune response to the formation of Aβ peptides and neurofibrillary tangles) is characterized by persistent activation of microglia and release of inflammatory mediators. Hence, an inflammatory cycle is perpetuated since microglia and astrocytes are constantly activated, leading to a further increase in the levels of cytokines and chemokines. These mediators, in turn, alter APP processing encouraging the formation of amyloid plaques. These alterations also result in reduced production of neuroprotective sAPPα. Senile plaques activate the complement system resulting in inflammation within CNS. Thus, neuroinflammation-mediated tissue damage initiates the degeneration process. During the early stages of AD, neuroinflammation leads to the entry of peripheral nervous system (PNS) cells with chemokine receptors into the brain crossing BBB [25]. As a result of Aβ deposition, chemokines e.g. CCL2, IL-8, CXCL10, CCL5 are released from PNS.

Amyloid plaques containing dystrophic neuritis, activated microglia and reactive astrocytes, along with released inflammatory mediators contribute to neuronal dystrophy. Inflammatory mediators and activated glial cells together kill neighbouring neurons and encourage amyloidogenic processing of APP. The inability of CNS phagocytes to clear amyloid plaques and upregulated formation of plaques as a result of chronic neuroinflammation play instrumental roles in AD [26]. In a cohort study, Taipa et al (2019) reported elevated levels of eotaxin, IL-1 receptor antagonist (IL-1ra), IL-4, IL-7, IL-8, IL-9, IL-10, IL-15, TNF-α, granulocyte colony-stimulating factor (GCSF), MCP1 and platelet-

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derived growth factor in CSF of AD patients in comparison with non-demented controls. The same study also reported inverse relations between CSF levels of IL-1β, IL-4, IL-6, IL-9, IL-17A, IFN-γ, basic fibroblast growth factor (basic FGF/ FGF2), granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, macrophage inflammatory proteins-1β and AD progression [27].

4.1. Proinflammatory cytokines

Cytokines are secreted by glial cells around Aβ plaques. Disturbances in inflammatory and immune pathways in AD have been strongly associated with altered levels of some acute-phase proteins and proinflammatory cytokines in the blood, CSF, and AD brains. Peptide Aβ itself can induce the expression of several proinflammatory cytokines such as IL-1β, IL-6, TNF-α and IFN-γ by glial cells. Proinflammatory cytokines like macrophage migration inhibitory factor (MMIF), YKL40, TNFs, and their receptors, sTREM2 are clearly engaged in TAU pathology and in the aging process [28]. IL-15, MCP-1, VEGFR-1, sICAM1, sVCAM-1, and VEGF-D are found to be associated with TAU pathology and correlate with CSF TAU level [29]. Proinflammatory cytokines induce indoleamine 2,3 dioxygenase to increase blood levels of quinolinic acid, a neurotoxic factor [30].

High levels of proinflammatory cytokines, such as IL-1β, IL-6, and TNF-α, have been detected in the brain of AD subjects [31]. Proinflammatory molecules produced by the reactive astrocytes can elevate the expression of secretases in neurons, enhancing the production of Aβ and activating microglia to produce inflammatory factors [32]. In transgenic mice model, proinflammatory cytokines viz. IL-1 β, TNF- α, IL-6, IL-12 and IL-23 have been found to correlate with amyloid load [33].

IL-1α and IL-1β initiate cell activation upon binding with cell membrane receptors. Elevated level of IL-1β is a characteristic feature of brain parenchymal cells immediately

 doi:10.20944/preprints202108.0237.v1

after injury [34]. IL-1 hastens neuronal degeneration by increasing the production of IL-6 and the activity of iNOS. In addition to that, IL-1 is also responsible for enhanced acetylcholinesterase activity, activation of astrocytes and microglial cells, expression of S100β, production of macrophage colony-stimulating factor (MCSF) and further additional production of IL-1. IL-6 is a major player in host inflammatory response. IL-6 displays neurotrophic effects by activating microglia, promoting astrogliosis and stimulating the production of acute-phase proteins. IFN-γ induces activities of TNFs and NO. TNF-α centrally regulates cytokine activities during inflammatory response through regulating an autocrine cascade of production of IL-1 and TNF-α from glial cells. In the AD brain, IL-1 regulates APP processing. In an experiment, rat cortical glia cells presented themselves with increased IL-6 mRNA on being exposed to the first 105 carboxy-terminal amino acids of APP [35]. Dose-dependent increments are observed in levels of IL-1, IL-6, TNF-α, MIP-1α and MCP-1 in glial cells on exposure to Aβ peptides [36].

4.2. Anti-inflammatory cytokines

While IL-1ra, IL-4, IL-6, IL-10, IL-11, IL-13, TGF-β act as anti-inflammatory cytokines, specific receptors for IL-1, TNF-α, and IL-18 act as inhibitors of proinflammatory cytokines. Anti-inflammatory cytokines belonging to Th2 and Th3 cell subsets exert a protective effect against AD by counteracting the effects of proinflammatory cytokines [9]. TGF- β, produced by Th3 cells is capable of ameliorating Aβ -induced cytotoxicity both *in vivo* and *in vitro* while deficiency of TGF-β1 promotes accumulation of Aβ peptides and formation of neurofibrillary tangles [37]. Dysregulation of the balance between proinflammatory and anti-inflammatory cytokines in the favour of proinflammatory cytokines lead to a cycle of further cytokine production, cytokine synergism and cellular activation ultimately amplifying and worsening neuroinflammatory conditions.

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IL-4, IL-10 and IL-13 can suppress proinflammatory cytokine genes e.g. IL-1, TNF and chemokines'. IL-1ra directly antagonizes the activities of IL-1α and IL-1β by competitive inhibition. Experimental results suggest that IL-1ra suppresses IL-1β-induced TNF-α production and iNOS expression in astrocytes by preferentially binding with IL-1R1[38]. In addition to protecting against IL-1β induced neurotoxicity, IL-1ra also attenuates neuronal damage caused by ischaemic excitations. IL-4 can suppress proinflammatory cytokines like IL-1, TNF-α, IL-6, IL-8 and MIP-1α by inhibiting their expressions. Further IL-4 is associated with increased production of IL-1ra and inhibition of IFN-γ leading to a decrease in TNF-α and NO. IL-10, acting through specific cell surface receptors reduces the synthesis of IL-1 and TNF-α. IL-10 also inhibits TNF-α, IL-1, IL-6, IL-8, IL-12, GMSF, MIP-1α, and MIP-2α Secretion of proinflammatory cytokines by glial cells is halted on pre-exposure to IL-10. IL-10 has been hypothesized to exert the actions by suppressing cytokine receptor expression, inhibiting receptor activation. TGF-β impedes the production of IL-2, IFN-γ and TNFs. Three mammalian isoforms of TGF-β i.e. TGF-β1, TGF-β2 and TGF-β3 are prevalent within the CNS. TGF-β is associated with a plethora of activities including microglial activation to inflammatory response, astrocytes, and regulation of COX-2 and APP. Interestingly, elevated levels of TGF-β1 and TGF-β2 have been observed in CSF and blood of AD patients [39,40].

4.3. APP protein

APP is a transmembrane protein present in the cell membrane of all neurons. Under normal conditions, α secretase and γ secretase cleaves APP into three fragments which in turn get digested via proteosomes (nonamyloidogenic pathway). During the initial phases of AD, the amyloidogenic pathway takes over and β secretase becomes involved in the process in place of α secretase [41]. α secretase activity is exerted by three members of A disintegrin and metalloprotease (ADAM) family viz. ADAM9, ADAM10 and ADAM17/ TNF-α converting

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enzyme (TACE). The β-secretase activity has been mainly attributed to the β-site APP cleaving enzyme. The γ-secretase complex comprises presenilin (PSEN), nicastrin, anterior pharynx defective-1 (APH-1), and presenilin enhancer-2 (Pen-2). The amyloidogenic pathway predominantly gives rise to fragments like sAPPβ, APP intracellular domain (AICD) and Aβ peptide spanning from 1-40 amino acid residues. These abnormal fragments are not digested resulting in extracellular accumulation of aggregates or plaques of those fragments. These senile plaques are termed β amyloids or Aβ lipoproteins. They, in turn, lead to neurotoxicity, apoptosis, oxidative stress and neuroinflammation. β amyloids, in addition to generating inflammatory responses, also cause mechanical disruption in synaptic transmission [42].

4.4. TAU phosphorylation

TAU protein stabilizes microtubules. Microtubules are very important for the cytoskeletal integrity of a cell. They reside throughout the axon to aid transport proteins move nutrients and neurotransmitters. Microtubules lose their structure in absence of TAU and break apart. When β secretase becomes more active than α secretase, a high amount of β amyloid is produced. β amyloid, in turn, causes hyperpolarisation of TAU protein through excessive phosphorylation of TAU [43]. On hyperpolarisation, TAU protein starts aggregating with each other. Unlike senile plaques, TAU clumps stay inside neuronal cell. As a result, the cytoskeleton starts to fall apart. Under this condition, axonal transport gets hampered. Neurotransmitter transport from soma to synaptic bud becomes affected and neuronal function decreases. Not only neurotransmitters, flow of nutrients inside the longest cell of the body would also suffer and gradually axons and dendrons would start to degenerate. Cluster of such neurons forms neurofibrillary tangles. Cytokines with kinase activity on TAU include cyclin-dependent kinase 5 (CDK5), glycogen synthase kinase-3β (GSK-3β) and p38 mitogen-activated protein kinases (p38-MAPK) [44].

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4.5. Glial cells

Progress in AD-related research has revealed important roles of glial cells like astrocytes, microglia, NG2 glia, and oligodendrocytes in the pathogenesis of the disease [45]. Astrocytes and microglia participate either by functioning as effector cells to release cytokines by somehow failing to live up to their homeostatic functions. NG2 glia, a novel and distinct class of glial cells in CNS are responsible for myelination and remyelination of axons thus playing a vital role in high-speed nerve impulse transport and cognition [46]. Amyloid peptides and their precursor APP protein act as glial activators. Disruption of the APP gene and its proteolytic products delay and decrease amyloid-dependent microglial activation.

Astrocytes are star-shaped glial cells in CNS involved in energy reserves, regulation of extracellular ions, as well as the clearance, metabolism of neurotransmitters, and modulation of oxidative stress. Neurotransmitter glutamate is released during neuroinflammatory conditions mainly which in the long-term is proved to be toxic to neurons via the excitotoxicity pathway. Astrocytes can take up glutamate and recycle it to neurons after transforming into glutamine, an amino acid [47]. During AD, Aβ peptides decrease uptake of glutamate, thus increasing oxidative stress. Interestingly, alongside the neuroprotective activities of astrocytes through Aβ clearance and degradation, they could also be a source of Aβ owing to their overexpression of BACE1 in response to chronic stress [48].

Migration of astrocytes to amyloid plaques is promoted by chemokines CCL2 and CCL3, which are released by activated microglial cells. Mouse astrocytes plated on amyloid-rich brain sections from APP transgenic mice have been found to reduce amyloids [49]. Astrocytes respond to CNS insults through a process named reactive astrogliosis, an early pathological feature of AD and can represent a response to the accumulation of amyloid and/or to the increasing number of degenerating neurons [50]. Astrocytes can be stimulated by oxidative stress, free saturated fatty acids, pathogens and lipopolysaccharides. Contrary to

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quiescent astrocytes, reactive astrocytes can produce cytokines, such as TNFα, IFNγ and ILs [51]. IFN-β, TNF-α and IL-1β, induce the generation of Aβ in primary human astrocytes and astrocytoma cells.

Astrogliosis is characterized also by a high level of the astrocyte marker glial fibrillary acidic protein (GFAP). The latter occurs around amyloid deposits both in the brain parenchyma and in the cerebral microvasculature. Senile plaques are associated with GFAP-positive-activated astrocytes. In various neuropathological states, the increased expression of GFAP corresponds to the severity of astroglial activation [52]. Microglial cells and astrocytes express pathogen recognition receptors e.g. toll-like receptors, integrin α6β1, A1, CD36, CD47, CD14 to act as class A scavenger receptors through DAMP [9].

Oligodendrocytes, under the influence of NG2 cells, are responsible for myelin sheath generation around axons. A study concluded that Aβ peptides induce local translation of myelin basic protein 18.5 kDa isoform in distal cell processes[53]. Aβ oligomers modulate the expression of myelin basic protein with the help of the integrin β1 receptor, Src-family kinase Fyn and Ca2+/CaMKII. The pharmacological inhibition of Fyn kinase can attenuate oligodendrocyte differentiation and survival induced by Aβ. In *ex vivo* organotypic cerebellar slices, Aβ caused upregulation of myelin basic protein through Fyn kinase and modulated oligodendrocyte population dynamics by inducing cell proliferation and differentiation [53]. Application of Aβ oligomers to cerebellar organotypic slices, enhance remyelination and oligodendrocyte lineage recovery in case of lysolecithin-induced demyelination.

4.6. Advanced glycation end products

Advanced glycation end products mediate crosslinking of certain proteins resulting in age-related decline in cognition and other cellular functions. RAGE, a ligand for both Aβ and S100B is also associated with the activity [54]. In hyperglycaemic patients, unusual glucose

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metabolism and oxidative stress aggravate the activities of advanced glycation end products. This may be correlated with the fact that; excess dietary carbohydrates and deficient cholesterol may lead to the development of AD. Intracellular neurofibrillary tangles and extracellular senile plaques serve as substrates for glycation. Advanced glycation end products induce the production of ROS and cytokines through activation of microglial RAGE leading to engagement of NFκB [55]. It has been clinically observed that low dietary intake of advanced glycation end products is directly related to reduced oxidative stress and inflammation [56,57].

4.7. Complement system

At an early stage of AD, Aβ peptides activate the complement systems. The complement system works as a part of the immune system to remove unwanted bodies through antibody-mediated phagocytosis. In course of doing so, complementary proteins interact with cell surface receptors to promote an inflammatory response in the host system. Complement system attacks and destroys invaders in four steps viz. recognition, opsonization, inflammatory stimulation, and killing. In the human brain, epicenter of complement activity lies within astrocytes. They can synthesize complement proteins like C1-C9, regulatory factors B, D, H, I and complement receptors like C1qR, C3aR and C5aR locally to defend through both classical and alternative pathways [36]. Microglia also supports phagocytosis by expressing C1q, C3 proteins and C1qR, CR3, C5aR receptors [58]. Apart from neuroglia, neurons also express regulatory factors H, S and receptors C1qR, C3aR and C5aR. Complement protein C1q affects the formation of amyloid plaques containing β-sheet structure [59]. In transgenic AD mice, inhibition of complement system by C3 knockout resulted in increased formation of amyloid plaques further supports a neuroprotective role of the complement system [59-61].

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5. Macrophage migration inhibitory factors in AD: pathogenic or protective?

MMIF, also termed as glycosylation inhibiting factor is classified as a proinflammatory cytokine being an important regulator of innate immunity. Expression of MMIF correlates with expression of VEGF in CNS [62]. Interestingly, glucocorticoids stimulate the secretion of MMIF whereas glucocorticoids are known to suppress most of the other cytokines. Thus, MMIF acts against the general anti-inflammatory response of glucocorticoids. There exists a debate on whether endogenous MMIFs support or counter the pathogenesis of AD. Enhanced MMIFs have been reported in mouse models of neurodegenerative disorders [9,63]. Again, several studies reported that MMIF knockdown in mutant mice has resulted in acceleration of neurodegenerative disorders [64,65]. MMIFs have also been reported to regulate neuroinflammation and autophagy in the favour of neuroprotection [63,66,67].

MMIF controls the synthesis and release of TNF-α, IL-1, and other cytokines. MMIF is also involved in macrophage functions like phagocytosis and tumoricidal activities. Brain insulin-resistant state arises due to prolonged exposure of cortical neurons to high concentrations of insulin. MMIF contributes to this insulin-resistant state through inhibition of phosphorylation of Akt [68]. In some cases, a structural homologue of MMIF, D-dopachrome tautomerase (MIF-2) exhibits synergistic activities in combination with MMIF [69]. MMIF and $A\beta_{1-42}$ fragments of senile plaques display similar neurotoxicity patterns. In another *in vitro* cell study, it was observed that ISO-1, an MMIF inhibitor successfully retracted neurotoxicity mediated by Aβ peptides further strengthening the correlation between Aβ and MMIF [70]. The study also reported enhanced MMIF levels in CSF of AD patients [70]. In another experiment, MMIF knockout successfully limited TAU hyperphosphorylation in the mouse model [71]. In silico studies suggest that MMIF may be involved in neuronal apoptosis during AD [72]. Interestingly, Popp et al (2009) did not find any difference in MMIF levels of AD patients with mild, moderate and severe dementia. In

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short, we can say that imbalance between oxidized and reduced isoforms of MMIF is the key to regulate the switch to either diseased or normal state [73].

6. Choroid plexus growth factors and AD

Growth-promoting properties of APP, along with other growth factors, play vital roles in the development of AD. Choroid plexus supports neuronal function by secreting CSF. VEGF and FGF can be found in epithelial cells of the choroid plexus. Choroid plexus is rich in various proteins and their receptors. Proteins include FGF-2, TGF-α and TGF-β along with mRNA expressions for TGF-β, IGF-II, FGF-2 receptors and NGF receptors. Choroid plexus also contains receptor binding sites for FGF-7, keratinocyte growth factor, insulin-like growth factor (IGF) 1 and IGF-2. Blood-CSF barrier made up of epithelial cells and tight junctions at choroid plexus allows selective passage of materials into the brain. FGF-2 has been reported to increase in brain parenchyma of AD patients. Infusion of FGF-2 in rat model has resulted in hydrocephalus *ex vacuo* which is a clinical feature of AD [74]. Improper CSF circulation and impaired clearance of CSF may give rise to dementia and neurodegeneration due to lack of nutrition to CNS cells and toxic accumulations within CSF.

6.1. Vascular endothelial growth factors

Vascular endothelial growth factors (VEGF) and their receptors have been reported to localize at the area with lesions and AD-related developments. Different isoforms of VEGF act as a proinflammatory-cytokine by increasing endothelial cell permeability, inducing expression of endothelial cell adhesion molecules and acting as monocyte chemoattractants [75]. VEGF is involved in the regulation of GLUT1 and tissue thromboplastin, which in turn regulate vascular pathologies of AD. GLUT1, present in BBB mediates glucose transport into the brain and reduced expression of GLUT1 is relatable with aggravated AD conditions. Tissue thromboplastin and derived factors play a proinflammatory role leading to vascular

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dementia [76]. AD patients tend to present with enhanced VEGF activity within reactive astrocytes [77]. Rats induced with astrogliosis displayed increased astrocytic and perivascular reactivity within the cerebral cortex [78].

6.2. Fibroblast growth factors

FGFs are circulatory proteins playing important roles to activate cell surface receptors. Around 23 FGF subtypes have been known to exert distinct functions till date [79]. Acidic FGF-1 and basic FGF-2, among eight other FGF family proteins, act through four families of FGF receptors. FGF-11 to14 do not act through FGF receptors.

FGF-1 and FGF-2 are more potent angiogenic factors than VEGF [80]. Within CNS, FGFs play the important roles in proper proliferation and differentiation of neuronal stem cells including neurogenesis and axonal growth. FGFs also support the self-renewal of radial glial cells. FGF-8 is a vital player for the proper functioning of the cerebral cortex. Increased levels of FGF-2 have reportedly been associated with AD brain leading to enlargement of ventricles [81]. FGFs regulate not only neuronal stem cells but also adult neurogenesis. Maintenance and survival of neurons throughout their lifetime depend greatly on FGF-2. Synaptic plasticity is, to some extent controlled by FGF-1 and FGF-2. Thus, proper conduction of nerve impulses through axons and synapses for proper cognition is dependent upon FGFs. Belluardo et al (2004) have demonstrated that upregulation of FGF-2 can successfully prevent neuronal loss in cortical and hippocampal regions of the brain [82]. In the rat models, FGF-21 has been found to ameliorate Aβ peptide-mediated neurodegeneration [83]. The effects were achieved via PP2A/ MAPK/ HIF-1α pathways interfering with TAU pathologies and minimizing oxidative stress [83].

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7. Neurotrophic factors

Neurotrophic growth factors, produced by neural stem cells are involved in the differentiation of cells and cell survival. Neurotrophic growth factors consist of NGFs, glial cell line-derived neurotrophic factor (GDNF), neurokines, and non-neuronal growth factors. NGF is probably the most discussed neurotrophic growth factor and neuropeptide primarily involved in the regulation of growth, maintenance, proliferation, and survival of certain target neurons. NGF was the first neurotrophin to be discovered followed by brain-derived neurotrophic factors, neurotrophin-3, neurotrophin 4/5, and neurotrophin-6 [84]. Neurotrophins bind to cognate Trk receptors and p75NTR receptors. The low-affinity neurotrophin receptor p75 can bind with all neurotrophin family members. Neurokines and cytokines related to interleukin-6 (IL-6) bind to cell surface receptor complexes, which share a common structural organization. The four ligands interchangeably employ two distinct receptor subunits, leukemia inhibitory factor receptor b (LIFR b) and gp130; some employ a ligand-specific α subunit [85].

NGF exhibits protective action over cholinergic neurodegeneration. NGF can influence APP processing towards the non-amyloidogenic pathway via protein kinase C coupled M1 and M3 receptors. Interestingly, NGFs are upregulated in AD patients' brain and CSF while NGF receptor TrKA is downregulated [36]. AD patients exhibit a higher phosphorylated TAU to Aβ peptide ratio compared to healthy individuals indicating towards the accumulation of NGF during the development of the disease. Brain-derived neurotrophic factors alone and in chimeric combination with NGF has been found to protect cholinergic neurons in prosencephalon [86]. AD brains have been diagnosed with decreased levels of mRNAs for brain-derived neurotrophic factors but normal levels of mRNAs for NGF and neurotrophin-3 [87]. In the AD brain, astrogliosis may contribute to increased NGF and reduced TrKA in the cortex and nucleus basalis. Vinculin-dependent adhesions are central to the functioning of NGF to promote axonal outgrowth. Vinculin-dependent coupling regulates

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the level of myosin needed for NGF stimulation. The role of NGF as a growth factor amongst a bouquet of proteins is paramount in cognitive processes that may be involved in the survival and phosphorylation of fibrils in axons, that are involved in AD and other chronic diseases closely related to AD [88].

8. Haematopoietic growth factors

Apart from controlling hematopoiesis in blood progenitor cells, hematopoietic growth factors like IL-3, GCSF, granulocyte macrophage colony-stimulating factor (GMCSF), MCSF, and erythropoietin play vital roles in the functional activation of all mature cells. In the biological and pathological role of the immune system, the immune system achieves its role by cells that encapsulate it as a whole. Such cells originate from hematopoietic stem cells in the bone marrow by a blood-forming process of hematopoiesis that give rises to myeloid progenitor cells and lymphoid progenitor cells [89]. Myeloid progenitor cells constitute megakaryocytes, erythrocytes, mast cells, and myeloblast. The myeloblast cells antithesize into immune cells, namely, basophil, neutrophil, eosinophil, and monocytes. Of the subset of the myoblast cells are the monocytes that later develop into macrophages, which play an initiating part in immune system responses that counter foreign material, pathogens, and compromised cells in the CNS.

Hematopoietic growth factors are important contributors to brain marrow for neuropoiesis. They can prevent neuronal death to some extent. Jin et al (2004) have pointed out enhanced neurogenesis during AD [90], though many pose doubts on the marker doublecortin [91,92]. In the mouse models, GCSF has been observed to restore cognition by restoring acetylcholine levels [93]. Stem cell factors, in combination with receptor c-kit stimulate neurogenesis [94]. Lower level of stem cell factor in blood and CSF indicate faster cognitive decline during AD [95]. Increased levels of angiopoietins 1 and 2 indicate cognitive a decline in AD. In the mouse models, angiopoietin 1 accelerates AD via FOXA2/PEN2/APP

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pathway [96]. Increased neurogenesis, anti-apoptotic influences, and mobilization of microglia contribute to brain repair involving hematopoietic growth factors.

9. Cytokines in the pathophysiology of AD: at a glance

Cytokines that mediate cell functioning, cell signaling behaviours, and neuro-immune activity are classified by the actions that they solicit. In the immune response, such cytokines are proinflammatory cytokines, anti-inflammatory cytokines and cytokines that inhibit virus replication. They can prevent neuronal death, macrophage-activating cytokines, B-cell activating cytokines, T-cell activating cytokines and mast-cell activating cytokines. In AD, certain cytokines are involved in the immune responses that precede and importune the actions of other cytokines in the innate neuroimmune inflammatory reactions that are observed in AD consequent of aberrant pathologies in the brain and concomitant to CNS insults such as, neurotoxicity, accumulation of Aβ senile plaque and TAU pathologies (Table 2). IL-1α containing plasmids were analysed in IL-1 cDNA clones by the hybrid selection of biologically active mRNA that resulted in abundant IL-1 in lipopolysaccharide-stimulated macrophages [97]. Of the classes of cytokines that are implicated in AD, specialized groups of cytokines are differentiated by the availability of their receptors expressed on the cell surface of implicated cell types and the condition of the genes that regulate these receptors.

Inflammation, inflammation-mediated expression of iNOS, and iNOS mediated release of NO play instrumental roles to degenerate neurons during AD [98]. In neurons, cytokines are believed to play a major role in routine neurological activities of the CNS in the transfer and reception of chemical cues that confer instructions on cell actions and reactions. Chemotactic cytokines that function as chemoattractant cytokines such as IL-8, IP-10) / CXCL 10 may experience N-terminal proteolytic alteration after being secreted. In AD where neurofibrillary tangles have been observed to be further propagated through the toxicity presented by Aβ plaque accumulation and loss of cholinergic neurons in rat basal forebrain

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primary septal culture [99]. Aβ prevented microtubule binding in primary cultures of fetal rat hippocampal neurons and human cortical neurons and induced hyperphosphorylated TAU at Ser-202 and Ser-396 isoforms accumulated in the somatodendritic compartment of Aβ treated neurons [100].

The constituents of axonal projections in the mammalian brain are, neurofilaments that form side projections of carboxy-terminals from the core filament believed to be heavily phosphorylated, and TAU-embellished microtubules that are known to be differentially phosphorylated. The α and β globulin subunits that constitute axonal microtubules are formed by the process of nucleation which is energy-consuming. An energy-expensive neuro-process would require optimal active mitochondria to properly conduct impulse. Hyperphosphorylation of TAU has been credited to play an acting role in the impairment of axonal support functioning to optimize communications amongst associated organelles interneuronally. NGF is a key growth factor in functional axonal growth and proliferation that is evident as important through other chronic and neurodegenerative diseases that adversely affect neuroimmune processes [101], therefore CNS coordination [102]. Similarly, to oxidative stress observed in AD brains that may lead to hyperphosphorylation of TAU. Where the absence of superoxide dismutase (SOD) was observed to increase oxidation damage from ROS; an escalation of Ser-36 phospho-TAU was revealed in treatments of SOD null mice; untreated mice did not survive past one week, SOD deficiency was therefore deleterious [103]. Notably, an increase in myosin IIB (MIIB) was also found to mirror the increasing depletion of SOD activity in chronically diabetic rats [104].

Symptomatic connections and similarities that exist between AD and other chronic diseases such as hypoxia and Parkinson's disease may underlie related mechanisms of similar pathways and molecular neurodegenerative mechanisms leading to those symptoms that may also be regarded as risk factors leading to encephalitis-like symptoms in early diagnosis of

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AD or presymptomatic MCI. Such symptoms include depression, depleted cognitive function, hallucinations, reduced glucose metabolism, sleep pattern changes, appetite changes, optophysiological decline, vision loss or blindness etc.

The growth factor VEGF was responsible for the permeability of cytokines and may serve as a permeability factor involve in the pathogenic scenarios. VEGF may consist of an AD-depression mediated mechanism of cognitive decline while neuroinflammation could possibly contribute to depression. Toll-like-receptors mediate the signalling of transcription factors that produced proinflammatory cytokines in microglial response in isolated and purified mouse brain tissue where TREM2 knockdown expressed an upregulation of TNF-α [105]. SORL1 increases the trafficking of APP to the cells undergoing the amyloidogenic pathway, thus contributing to the development of AD.

9.1. Cytokines and BBB

There exists a definite correlation between brain cytokine levels and neuropsychiatric disorders. Right at this point, selectivity and integrity of BBB to cytokines become important. Cytokines are pleiotropic, hence their release, unlike hormones has more complicated effects on the regulation of neurotransmission. They can cross BBB, activate free calcium, and by disrupting the compartmental model of brain calcium homeostasis, compromise the integrity of BBB [12]. Many cytokines can pass through BBB directly [106]. Glial cell-derived neurotrophic factors bypass the BBB by simple diffusion through circumventricular organs. Passage of IL-1α, IL-6, and TNF-α involves saturable influx transport through retrograde axonal transport system [12,107]. TNF-α, a downstream cytokine of chemokine IP10 decreases tight junction proteins leading to the destruction of endothelial tight junctions of BBB to affect its permeability [108,109]. Inhibition of mTOR hyperactivity has been reported to protect the integrity of BBB in AD [110]. BBB dysfunction brings about early aging in the brain paving the way for AD and other neurodegenerative disorders.

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10. Potential strategies involving cytokines for management of AD

AD affects millions of individuals worldwide among the aging population, yet no therapeutic intervention is available to stop and eliminate this disorder. Neuropathological hallmarks of AD are extracellular deposits of Aβ peptides assembled in plaques, intraneuronal accumulation of hyperphosphorylated TAU protein forming neurofibrillary tangles and chronic neuroinflammation. No absolute cure for AD is available till date [111].

Cholinesterase inhibitors and NMDA antagonists display moderate relief in the case of AD. Donepezil, an inhibitor of acetylcholinesterase improved cognitive conditions in AD and increased brain-derived neurotrophic factors [112]. Pharmacotherapy against Aβ and TAU have yielded limited success only. Treatment with β-sheet breaker peptides results in reduced brain inflammation by disrupting amyloids [113]. RAGE/NF-κB axis could be a potential therapeutic target in AD [114]. Some dietary nutraceuticals display inhibitory effects on the formation of advanced glycation end products [115]. Resveratrol has been found to modulate levels of β-amyloids and certain inflammatory markers in AD patients [116]. Luteokin can play a prophylactic role against AD [117]. Moderate activation of microglia is thought to have beneficial effects in removing neurotoxins, cellular debris, or dying cells, and also in promoting neuronal survival. Since MMIF is augmented in AD, measuring blood and CSF levels of MMIF may represent a diagnostic biomarker useful both for diagnosis and therapeutic monitoring of the disease [118]. Moderate activation of microglia by acute neuroinflammation is thought to have beneficial effects in removing neurotoxins, cellular debris or dying cells and also in promoting neuronal survival [119]. IL-1 ra, a glycosylated protein antagonizes the cell activating action of IL-1. TNF-α has been reported to possess neuroprotective effects [120]. TGF-β is capable of converting an active site of inflammation into one dominated by reparations [121]. Kitazawa et al (2011) described that blocking IL-1 signalling in 3xtg AD mice with an IL-1 receptor blocking

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antibody was beneficial, since it leads to a decrease in certain Aβ fibrillar forms and plaques [122].

It has been suggested that a blockade of the ongoing inflammatory processes may delay the progression of AD [123]. Studies suggest lesser incidents of arthritis patients receiving NSAIDs regularly developing AD [124,125]. The fact that COX-2 mRNA is upregulated in AD brain, further supports this claim. Receptors for hematopoietic growth factors expressed on neurons provide novel targets for drug discovery in the search for agents that can reverse the progression of AD.

It is interesting to observe that peripheral phagocytes can effectively clear plaques and therapeutic strategies aiming at favoring the recruitment of these cells into the CNS are actively being pursued [9]. In the mouse models, the brain-derived neurotrophic factors have improved AD conditions by delaying synapse loss, improving cell signalling and improving cognition and spatial learning [126]. GCSF and analogues have proven neuroprotective activity which may possibly be used therapeutically. *In vivo* intra-peritoneal VEGF administration reduced cognitive impairment in the mice model of AD [127]. As discussed earlier, NGFs are potential candidates for significant improvement of cognitive functions. Biogenetic exosome-mediated activation of microglia and deregulation of microRNA can be useful to fight to neuroinflammation [128]. Erythropoietin, together with NFκB can prevent neuronal injury triggered by β-amyloid toxicity [129]. Inhibitors of TNF-α have exhibited potential promise to slow down the progress of AD-associated cognitive decline [130]. Experimentally, improvements have been observed in patients by delivering mature NGFs into the AD brain [88]. ApoE4 centric treatment approaches are gaining interest in recent times since ApoE4 is involved in more than 50% of AD cases [131]. M2 microglia are generally engaged in the restoration of homeostatic balance after an inflammatory insult by releasing anti-inflammatory factors. Thus, the therapeutic promise is there to prevent and

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treat neuroinflammation with protective functions of microglia [132-134]. Another potential strategy might be to inhibit BACE1 to reduce the production of Aβ, however, clinical success is yet to be achieved [135]. Recently, multitarget-directed ligand-based treatment strategies have started to evolve centering on inhibition of glycogen synthase kinase 3β, a crucial enzyme for TAU hyperphosphorylation, and some other CNS specific signalling pathways [44]. Nowadays, in the war against AD and associated disorders, researchers are focussing more on regulating neurotransmitters, lipid metabolism, autophagy, circadian rhythm, gene therapy etc. [136].

11. Conclusion

In this review, ample evidence collected reflects some of the roles of cytokines and growth factors in the pathogenesis of AD and pathologically related in AD-like neurodegenerative conditions that help understand the propensities and action of cytokines and factors regulating their effects on neuron upon apoptotic decline. Altogether, evidence evinced in previous research on the rather novel concentration on the topic of cytokines in neuroimmune system responses and their role in inflammation possibly preceding neurotoxicity and intra-thecal generation of immune molecules and cytokine-producing cells show that cytokines mediate and even activate innate neuroimmune agents. Cytokines regulate levels of proinflammatory and anti-inflammatory populations to maintain CNS machinery homeostasis [137]. Proinflammatory cytokines induce inflammation in AD and AD-like pathogenesis in response to the apoptotic scenarios where some growth factors implicated are involved in the expression of cytokinetic reactions to activate microglia that cause inflammation in AD. Cytokines and growth factors such as NGF, VEGF, TNF-α, IL-1 additionally impact intricate

molecular processes necessary for balance and homeostasis in cognitive mechanisms. To conclude, there exists ample scope of improvement regarding clinically useful strategies to mitigate AD.

Author Contributions: GO, SD, VDF and RK contributed to the conceptualization and designing the manuscript. VC, VKK, AC, UA, JV, PG, HPRP, KDG, PHR edited and corrected the manuscript. The final correction and editing were done by GO, SD, VDF, and RK.

Funding: V.D.F provided APC for publishing this manuscript and all the authors acknowledged the same.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors are thankful to the Council of Scientific and Industrial Research, New Delhi, India, for awarding research project (grant number 02(0275)/16/EMR-II) to Saikat Dewanjee. Authors sincerely acknowledge Jadavpur University, India, CSIR-Indian Institute of Chemical Technology, Hyderabad, India, for providing necessary facilities, and DBT-India for providing Ramalingaswami Re-entry Fellowship to Ramesh Kandimalla (RK) for the period of 2018-2023 (No. BT/RLF/Re-entry/22/2016 and SAN.No. 102/IFD/SAN/1117/2018-19).

Conflicts of Interest: The authors declare no conflict of interest.

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Legends to the Figures

Figure 1. Schematic diagram showing GCSF (Granulocyte colony-stimulating factor) role in promoting neural network survivability via its entry through BBA and regulation of GCSF and LEF1 availability. VEGF increased BBB permeability, however, a defective VEGF expression can promote immunoreactivity and characteristic of AD.

Figure 2. Schematic diagram showing mild cognitive impairment (MCI) characterized by an upregulation of IL1β and $A\beta_{42}$ expressions, which was found to be linked with an upregulation of TNFα and a decrease in TGFβ.

Figure 3. Schematic diagram showing impact of LPS on elicited CCL2 activity that promote Activin A-factor and causes synaptic impairment that subsequently contributes to an aberrant hippocampal plasticity.

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Figure 4. Proinflammatory cytokines and chemoattractant cytokines are key characteristic of neuroinflammation that can be acquired by the activation of microglia and can escalate neurodegeneration. Abnormalities in the TREM2 variant lead to defective microglia activation and decrease in its phagocytic ability.

Figure 5. Schematic diagram showing that an absence of CX3CL1 (chemokine) increases LPS response and leads to an increase in TNFα (proinflammatory cytokine) expression. TNFR1 regulates CPLA2 and could stimulate arachidonate release. Arachidonate release can further led to IL1 release from macrophages under LPS stimulation.

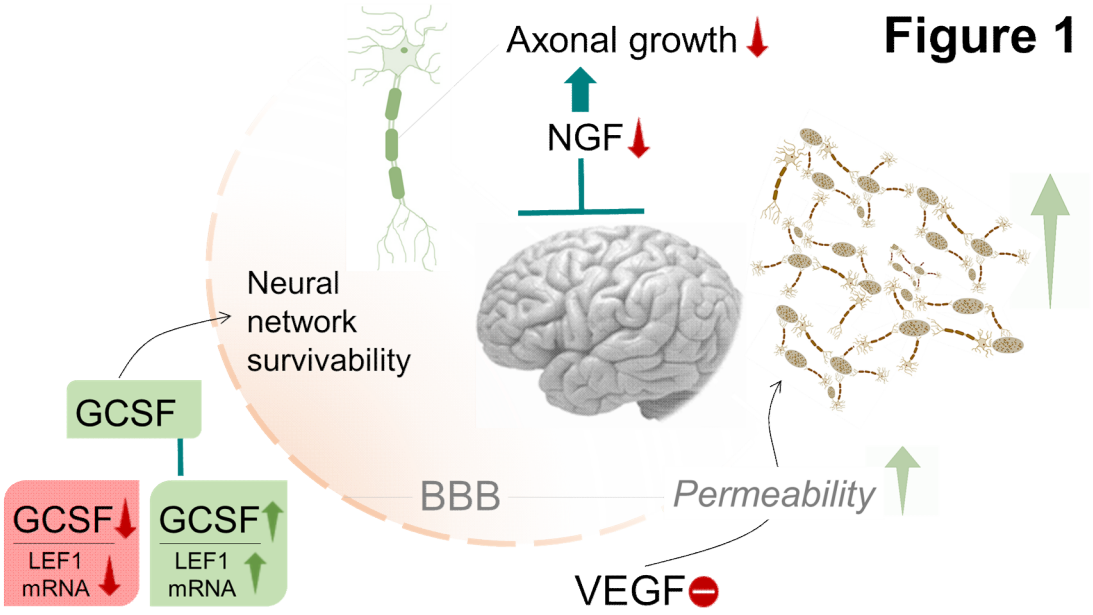

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Figure 2

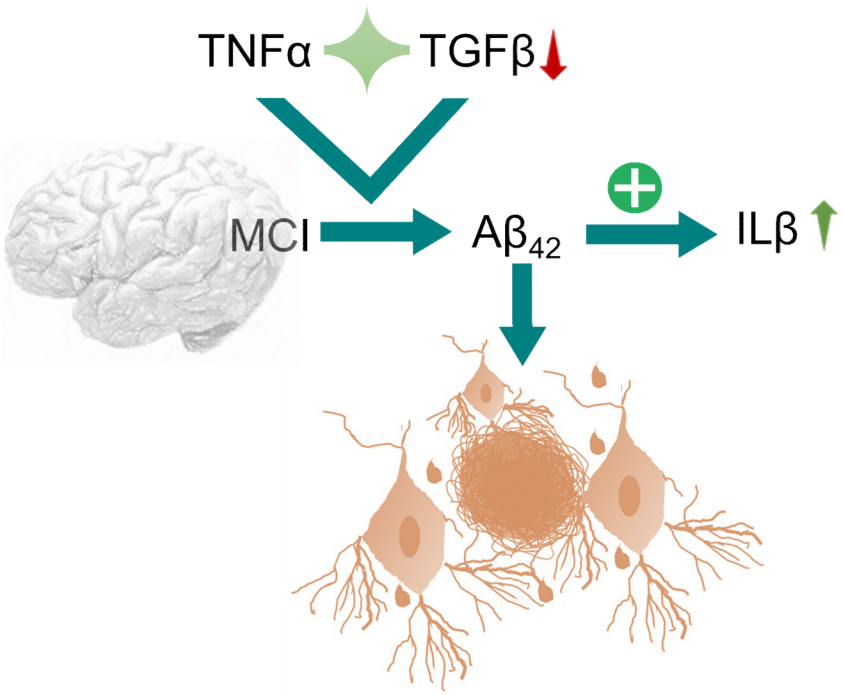

Figure 3

Figure 4

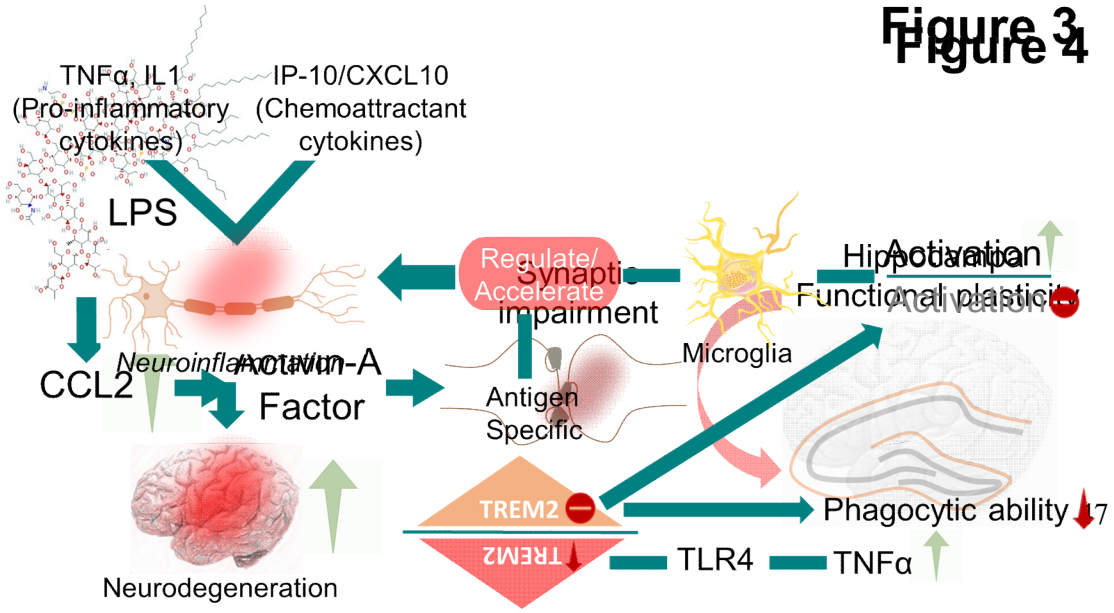

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Figure 5