

Review Article

Glycogen Synthase Kinase-3 β : A Mediator of Inflammation in Alzheimer's Disease?

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Proliferation and activation of microglial cells is a neuropathological characteristic of brain injury and neurodegeneration, including Alzheimer's disease. Microglia act as the first and main form of immune defense in the nervous system. While the primary function of microglia is to survey and maintain the cellular environment optimal for neurons in the brain parenchyma by actively scavenging the brain for damaged brain cells and foreign proteins or particles, sustained activation of microglia may result in high production of proinflammatory mediators that disturb normal brain functions and even cause neuronal injury. Glycogen synthase kinase-3 β has been recently identified as a major regulator of immune system and mediates inflammatory responses in microglia. Glycogen synthase kinase-3 β has been extensively investigated in connection to tau and amyloid β toxicity, whereas reports on the role of this enzyme in neuroinflammation in Alzheimer's disease are negligible. Here we review and discuss the role of glycogen synthase-3 β in immune cells in the context of Alzheimer's disease pathology.

1. Inflammation in Alzheimer's Disease

In addition to progressive loss of neurons and accumulation of intra- and extracellular protein deposits, chronic inflammation is a major pathological hallmark of Alzheimer's disease (AD) [1, 2]. Neuroinflammation in AD is characterized by the existence of inflammatory mediator cells surrounding the β -amyloid (A β) plaques and sites of neuronal injury [3–5]. Even though microglia, the main immune cells of the brain, have been extensively studied in AD, the exact role of inflammation in the disease pathogenesis remains elusive [3–10]. There is substantial evidence that microglia and the monocytic cells derived from the blood or bone marrow at least initially protect neurons from neurotoxic accumulation of A β and even release neurotrophic factors and extracellular proteases which may support neuronal survival and regeneration [5–11]. On the other hand, extensive and long-term release of proinflammatory mediators and reactive oxygen or nitrogen species (ROS and RNS) by the inflammatory

cells is thought to accelerate neurodegeneration and disturb cognitive functions [3–10].

The primary inflammatory cells in the central nervous system are microglia, constituting around 10% of all cells in the brain. They represent the innate immune system and form the first line of defense against invading pathogens in the brain [12–14]. Microglia serve as sensors for disturbed brain tissue homeostasis as they accumulate and proliferate locally in response to neuronal injury or penetration of foreign material in the brain [13, 14]. In AD, such activation can result from extracellular deposition of A β , neuronal injury caused by A β or tau toxicity [5–15], to some extent from ischemic or traumatic brain injury, and may be contributed even by local or systemic infection [16, 17]. In addition to microglia, astrocytes, pericytes, endothelial cells and neurons are thought to play a role in inflammatory responses relevant to AD [18]. However, most of the data on the impact of inflammation in AD originate from studies with microglia.

2. Glycogen Synthase Kinase 3- β in the Nervous System

Glycogen synthase kinase 3 (GSK-3) is a multifunctional serine/threonine kinase present in all eukaryotes. There are two highly homologous isoforms of GSK-3, GSK-3 α and GSK-3 β , that are usually equivalent in actions. In addition, there is an alternatively spliced GSK-3 β variant that encodes GSK-3 β 2, which has a 13-residue insert in the kinase domain [19–25] and is expressed exclusively in the nervous system [19–25]. GSK-3 shows partial constitutive activity and is known to phosphorylate more than 50 different substrates. The most important mechanism for regulation of GSK-3 β activity is inhibitory phosphorylation of Ser9 by protein kinase A (PKA) protein kinase B (PKB)/Akt and protein kinase C (KPC). Other kinases may phosphorylate the regulatory Ser9 as well. Activation of GSK-3 β is enhanced when also the regulatory Tyr216 is phosphorylated [19–25].

In the brain, GSK-3 β is known to be involved in neurogenesis, neuronal migration, neuronal polarization, and axon growth and guidance. GSK3 β 2 shows the highest expression in the nervous system during development and seems to have a special role in neuronal morphogenesis [25–32]. GSK-3 β affects axon growth by controlling microtubule dynamics through phosphorylation of microtubule-associated proteins (MAPs) such as Tau, MAP-1B and adenomatous polyposis coli [25–32]. Importantly, GSK-3 β plays a key role in neuropathology of AD, schizophrenia, autism and Parkinson's disease (PD). Also, the polymorphisms in GSK3 β interact with the microtubule-associated protein Tau (MAPT) haplotypes to increase the risk for idiopathic PD and AD [32–35].

There is substantial evidence that activation of GSK-3 β contributes to tau pathology, A β synthesis, and apoptotic neuronal death and it is thus not surprising that GSK-3 β has been recognized as a potential therapeutic target in AD [35–37]. However, GSK-3 β is a well-known regulator of innate and adaptive immune responses and plays a key role also in pathways of microglial activation relevant to AD [19, 20, 38–41]. Considering that neuroinflammation is a characteristic of AD brain pathology, the role of GSK-3 β in glial cells is of great interest. The therapeutically interesting role of GSK-3 β in regulating inflammation in AD is emphasized by the fact that various forms of A β promote microglial activation and release of proinflammatory mediators and ROS/RNS. In addition, *in vitro* studies suggest that microglial activation may in turn induce accumulation of tau in neurites through microglial ROS production [15].

3. GSK-3 β and Migration of Microglia

Migration of blood and bone marrow-derived monocytic cells as well as endogenous microglia to the sites of brain injury and abnormal proteins, such as A β , is a necessary step before production of proinflammatory mediators or neurotoxins and attempts of phagocytosis [10, 11, 13, 42–48]. GSK-3 β has been reported to be a key kinase regulating migration of various cell types, such as different stem cells

and other cells related to development, cancer cells, endothelial cells, and blood-derived inflammatory cells [39, 49–52]. Similarly, GSK-3 β has been shown to promote microglial migration both *in vitro* and *in situ* [39]. When random and directed migration of BV2 cells were studied using transwell migration and scratch assays, respectively, GSK inhibitors were found to inhibit both types of microglial migration by far more than 50% [39]. The same authors also demonstrated that GSK-3 β mediates migration of endogenous mouse microglia in response to slice injury of hippocampus [39]. It is possible that GSK-3 β promotes migration/mobility of microglia at least partially by triggering upregulation of CD11b, the α M β 2 integrin and complement receptor, which are needed for adhesion and migration of leukocytes, including microglia [23]. Studies on the role of GSK3 in migration of other cell types support the conclusion that GSK-3 β controls multiple pathways involved in migration [28, 30, 51, 53].

4. GSK-3 β and Microglial Inflammatory Cytokines, Chemokines and Reactive Oxygen/Nitrogen Species

The production of proinflammatory molecules is a crucial feature of cells needed for innate immune response and the most widely investigated function of microglia in neuroinflammation coupled to AD. Microglia are able to secrete a variety of cytokines and chemokines upon activation by A β . These include interleukin 1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor alpha (TNF- α), as well as chemokines such as macrophage inflammatory protein-1 (MIP-1) and monocyte chemoattractant protein-1 (MCP-1) [54]. These secretory products have been postulated to contribute to neuronal death seen in AD brain. In general, cytokines function by regulating the intensity and duration of the immune response [55, 56]. Thus, IL-1 can induce IL-6 production and stimulate synthesis and release of nitric oxide by triggering inducible nitric oxide synthase (iNOS) [57]. This neuroinflammatory stimulation of microglia is further characterized by activation of the complement cascade and induction of the prostanoid generating enzyme cyclooxygenase-2 (COX-2) [57–60]. In addition to this general proinflammatory role, A β -induced release of cytokines may promote further A β production in microglia. Certain cytokines, such as IL-1, can interact with the amyloid precursor protein (APP) processing pathway resulting in increased cleavage of A β [61]. In turn, fibrillar A β has been reported to increase neurotoxic secretory products, proinflammatory cytokines and RNS/ROS [5–7]. Eventually, these interactions between cytokines and APP processing establish a self-propagating cycle of neuronal injury [62, 63]. Indeed, several lines of evidence suggest that continuous cytokine production and inflammation-driven cascades cause further activation and recruitment of microglia and can exacerbate disease progression or even sensitize to AD pathology [8, 9]. This continuous reactive microgliosis has been described as the cycle of neuronal death: as in AD brain the cause (A β) of microglial activation is not effectively cleared, microglia

may enhance their secretion of inflammatory mediators and thus promote toxicity to nearby neurons. However, the causal relationship between microglial activation, cytokine production, A β accumulation and neuronal death has not been completely resolved [14].

It is important to note that microglia have also a potential beneficial role in neuroinflammation when another general category of cytokines are released. These antiinflammatory cytokines include IL-1 receptor antagonist (IL-1Ra), IL-4, IL-10, and tumor growth factor beta (TGF- β) [64–68]. IL-4 and TGF- β have a potential to reduce the expression and activity of CD40 and class II MHC [69]. TGF β has also been reported to reduce A β burden in the brain parenchyma in a transgenic mouse model of AD [64]. On the other hand, IL-4 can counteract AD pathology by selectively inducing the clearance of oligomeric A β by primary microglia [64, 65]. Similarly, IL-10 can reduce proinflammatory state of microglia by inhibiting the synthesis of cytokines TNF α , IL-1, IL-6, IL-12, granulocyte-macrophage colony stimulating factor (GM-CSF) and chemokines MIP-2, MCP-1 and RANTES [66, 67, 70].

5. Signaling of GSK-3 β in Inflammation

GSK-3 β is a major regulator of the balance between the above-mentioned proinflammatory and antiinflammatory mediators in immune cells, including microglia [38, 39]. This regulation is manifested by multiple pathways and include interactions with nuclear factor κ B (NF- κ B) and mixed lineage kinase 3 (MLK3)/c-Jun N-terminal kinase (JNK) signaling pathways [38, 39, 49] (Figure 1).

NF- κ B is a dimer protein complex that controls the DNA transcription. In resting microglia, the NF- κ B dimers are sequestered in the cytoplasm by inhibitors of κ B (I κ Bs) [71]. Activation of the NF- κ B is triggered by the signals that result in degradation of I κ B, thereby freeing the NF- κ B complex to enter the nucleus and interact with the DNA binding sites of NF- κ B [72, 73]. Activation of NF- κ B mediates expression of several proinflammatory cytokines and iNOS [74]. Once activated, NF- κ B transcriptional activity is further regulated by inducible posttranslational modifications, including phosphorylation and acetylation [49, 75–80]. In certain conditions, GSK-3 β may regulate NF- κ B activation by phosphorylation of p65 subunit of NF- κ B upon TNF α treatment, whereas in cultured microglia LPS treatment induces NF- κ B activation by increasing acetylation of p65 at lysine 310 through GSK-3 β [49, 75–80]. In fact, several studies support the idea that such acetylation of p65 is required for the full transcriptional activity of NF- κ B and that GSK-3 β increases the p65 binding of the coactivator CREB-binding protein (CBP), which has acetylase activity. CBP is present in limited amounts and also binds and acetylates transcription factor CREB. Thus, these two transcription factors, the p65 subunit of NF- κ B and CREB, compete for CBP and activation of GSK-3 β pathway shifts the balance in favor of NF- κ B [20, 49, 75–80]. The GSK-3 β -mediated increase in NF- κ B activity results in expression of proinflammatory cytokines and chemokines, such as TNF α ,

IL-6 and MCP-1. Simultaneously, the expression of IL-10 is reduced, partially because of the reduced DNA binding activity of CREB and also AP1, which are the main transcription factors contributing to IL-10 expression. The eventual proinflammatory effect of GSK-3 β signaling is mediated by reduced IL-10 expression, which leads to further increased synthesis of various cytokines and chemokines [20, 49, 75–80].

β -catenin is a transcriptional coactivator of WNT signaling and a direct target of GSK-3 β phosphorylation. β -catenin regulates cell proliferation and inhibits NF- κ B [81, 82]. Upon GSK-3 β phosphorylation, β -catenin enters the proteasomal degradation pathway resulting in reduced inhibition of NF- κ B and thereby increased NF- κ B-mediated inflammatory responses [81, 82]. β -catenin expression is increased in microglia of transgenic AD mice and Wnt signaling has been reported to play a role in impaired cognitive functions in transgenic AD mouse models [83, 84].

Activation of IL-6 receptors executes proinflammatory response through activation of STAT3 transcription factor, leading to increased expression of proinflammatory molecules, including IL-6 itself. GSK3 β selectively promotes STAT3 and STAT5 activation and thereby IL6-induced proinflammatory responses [38, 49, 85].

Finally, certain proinflammatory responses, such as the LPS-induced activation of microglia involve JNK pathway that is regulated by MLK3. GSK-3 β phosphorylation may be needed for proper function and dimerization of MLK3, which eventually leads to increased activity of JNK pathway and TNF- α synthesis [49, 86].

Even though there is substantial evidence for proinflammatory role of GSK-3 β in several cell types, including microglial cell lines and primary rodent microglia, there are also studies demonstrating an opposite role for GSK-3 β . The contradictory results most likely reflect the dependence on the type of cell, stimulus and experimental conditions as the targets of GSK-3 β phosphorylation are numerous and of interacting signaling pathways [87–89].

6. GSK-3 β and Phagocytosis

Phagocytosis is a main function of microglia. In vitro microglia have the capacity to phagocytose A β , but several studies have failed to show actual A β -laden vesicles in microglial cells in animal models of AD or in AD [4, 11, 64]. At least the capacity of successful phagocytosis by microglia is very limited in AD brain and not sufficient to prevent the formation of A β plaques [4, 11, 64]. However, modulation of microglial activity may enable microglia to effectively phagocytose A β as evidenced by activation of microglia for example by A β opsonisation [90, 91]. In models of AD, the pathway resulting in A β phagocytosis is initiated when A β binds a complex of microglial surface receptors consisting of the $\alpha_6\beta_1$ integrin, CD36, CD47, and the class A scavenger receptor (SRA) [10]. In addition, Toll-like receptors (TLRs) which function as dimers and are often coupled to CD14 coreceptors, functionally interact with other partners of the microglial A β binding receptor complex [92–96] and

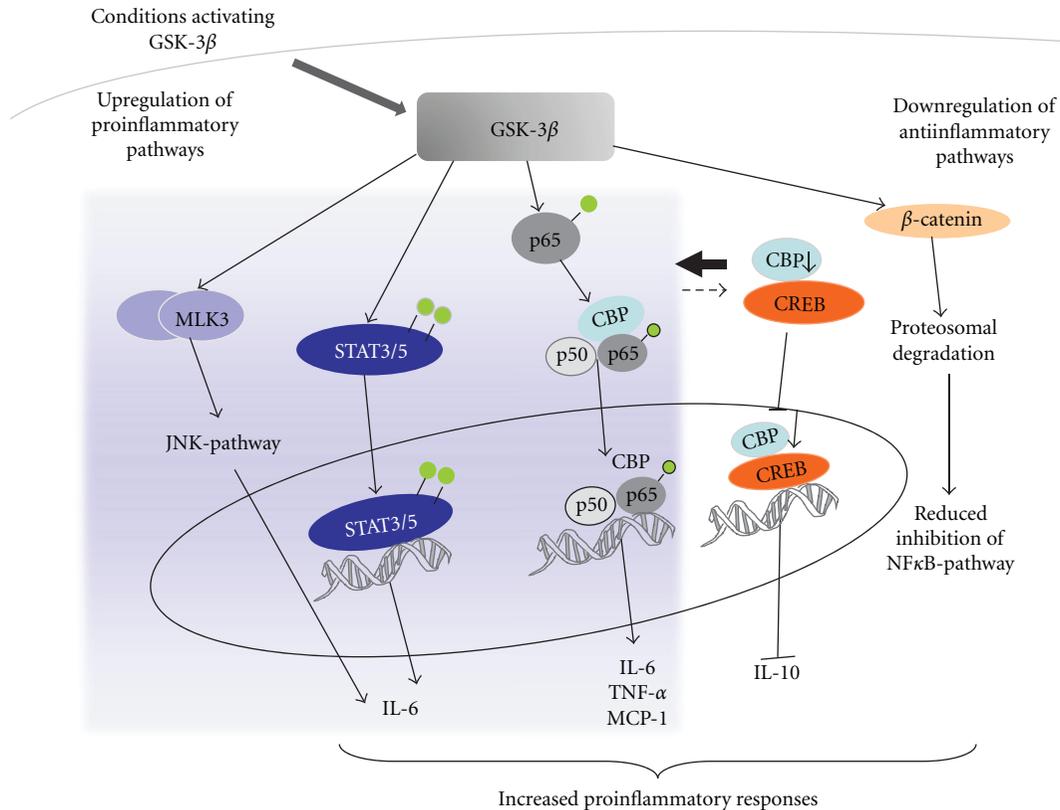


FIGURE 1: GSK-3 β regulates the production of microglial inflammatory molecules. GSK-3 β activation has been shown to increase the production of proinflammatory mediators via multiple mechanisms. GSK-3 β is able to activate JNK-, STAT3/5- and NF- κ B pathways leading to increased cytokine and chemokine production. GSK-3 β is able to increase the binding of coactivator CREB-binding protein (CBP) to p65 thus enhancing NF- κ B mediated transcription. Since CREB competes for CBP binding, activation of GSK-3 β shifts the balance in favor of NF- κ B pathway and CREB-mediated induction of IL-10 is reduced. Moreover, GSK-3 β activation leads to proteosomal degradation of β -catenin, thus resulting in reduced inhibition of NF- κ B-activation. All these events lead to enhanced production of proinflammatory molecules.

execute phagocytosis associated with increased ROS. In turn, engagement of this receptor complex activates tyrosine kinase-based signaling cascades [10, 97, 98] resulting in beneficial phagocytosis but also in production of reactive oxygen species (ROS) and secretion of cytokines [99, 100].

The role of TLR2 and TLR4 in A β phagocytosis and AD is emphasized by numerous studies. The expression of TLR2 and TLR4 receptors are upregulated in both AD brains and in related transgenic mouse models of AD. Also, the microglia associated with A β plaques show increased levels of mRNA coding for TLR2, -4, -5, -7, and -9 [101]. In addition, AD mice deficient in TLR4 show increased brain A β burden. Stimulation of microglial cells with TLR2 and TLR4 ligands boosts indirect clearance of A β *in vitro* [102]. Moreover, induction of monocyte recruitment in response to foreign particles, including A β , may require activation of TLR2-based signaling pathway. Gene delivery of TLR2-lentivirus into the bone marrow cells can rescue the cognitive decline of TLR2 deficient AD mice [103]. Upon A β stimulation, monocytes from normal subjects upregulate TLRs, whereas monocytes from AD patients may fail to do so [104]. Also, the level of TLR4 in monocytic cells of AD patients may be lower compared to levels of TLR4 in the same cell population of

healthy controls. Finally, bisdemethoxycurcumin, an anti-inflammatory compound, improves the defective clearance of A β and the transcription and translation of TLR2-4 in monocytic cells of AD patients [104]. These studies point to the importance of TLR signaling in the phagocytic activity of blood-derived monocytic cells in AD.

Signaling of several TLRs, including TLR2, TLR4, TLR5, and TLR9 is regulated by GSK-3 β in human monocytes and is coupled to production of cytokines [39, 41, 105] (Figure 2). Stimulation of TLR receptors activates phosphatidylinositol 3-OH kinase (PI(3)K) pathway activated Akt leading to phosphorylation and inhibition of GSK-3 β . As a result, the cells produce less proinflammatory molecules but upregulate production of anti-inflammatory cytokines, such as IL-10 [105].

Another pathway relevant for A β clearance is triggered by activation of CD40R, a transmembrane receptor of the TNF gene superfamily that is expressed on a variety of cells, such as monocytes, B-cells, antigen presenting cells, endothelial, smooth muscle cells, fibroblasts, and microglia [50]. CD40L is an immunoregulatory molecule that is expressed by activated T-cells, for example. By preventing the CD40-CD40L interaction in AD transgenic mice [106, 107] the A β burden

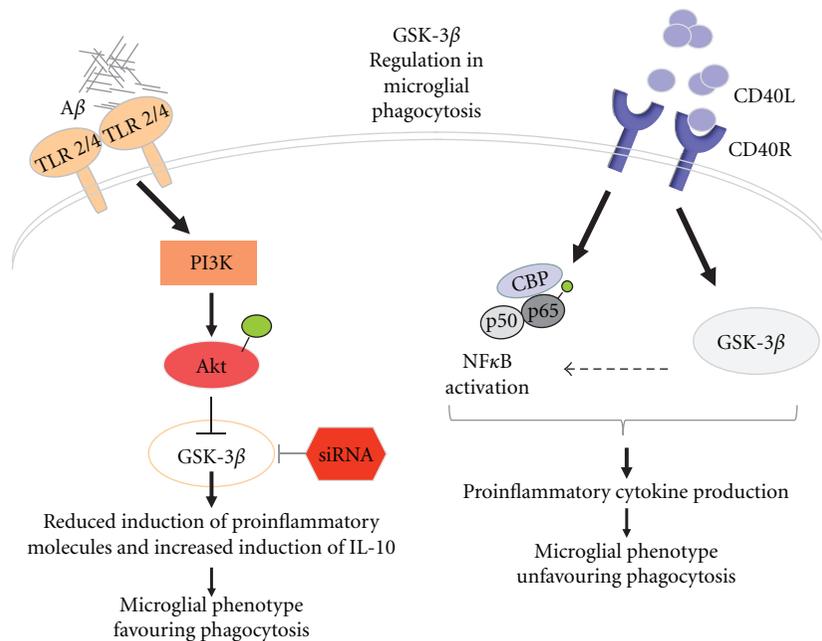


FIGURE 2: GSK-3 β in the regulation of microglial phagocytosis. Microglial phagocytosis has been shown to be enhanced through activation of TLR2/4 pathway. Binding of A β to TLR2/4 may result in activation of PI3K signalling eventually leading to inhibition of GSK-3 β activation. This in turn shifts the cellular balance towards increase in the production of antiinflammatory cytokines favouring phagocytic microglial phenotype. On the other hand, CD40R-CD40L interaction results in both NF- κ B and GSK-3 β activation thus increasing proinflammatory cytokine production. This may shift the phenotype of microglial cells being less capable of clearing A β .

is reduced. A β stimulation in the presence of CD40-CD40L interaction has been demonstrated to cause diminished microglial phagocytosis and a shift in balance towards an adaptive, antigen-presenting state [108]. It is conceivable that CD40R is activated in microglial cells in AD. The interaction between CD40 and CD40L enhances the expression of cytokines, chemokines, matrix metalloproteinases, growth factors, and adhesion molecules, mainly through the stimulation of NF- κ B and also by GSK-3 β , which has a role in CD40-mediated response and polarization of naive CD4+ T cells to Th2 cells [50, 51].

7. Concluding Remarks

Inflammation and especially microglial activation is a contributory factor in neurodegeneration, including AD. Without question, GSK-3 β is a central mediator molecule of harmful inflammatory mechanisms relevant to AD. Several studies convincingly link the role of tau and A β to increased activity of GSK-3 β in the brain [109–114]. Indeed, both human and rodent model studies on AD indicate that inhibition of GSK-3 β can be expected to be beneficial in AD [115–120]. Even though some small molecules inhibiting GSK-3 β reduce memory/learning deficits and also inflammation in transgenic mouse models of AD [115–120], the link between GSK-3 β and harmful inflammation in AD has not been much explored. There are hardly any investigations on the A β or tau-related harmful inflammation through mechanisms involving GSK-3 β . Based on the overall literature on

inflammation, microglia, and AD, we hypothesize that GSK-3 β is a potential therapeutic target uniting A β deposition, tau aggregation, and inflammation, which represent all the key components of AD pathology.

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