

Pathogenesis of Alzheimer’s Disease: Interactions Among Glial Cells, Inflammasomes, Caspases, and Signaling Pathways & Implications for Personalized Treatment

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Abstract

Alzheimer’s Disease (AD) is a progressive and irreversible neurodegenerative disorder that slowly destroys one’s memory and thinking skills and is traditionally associated with amyloid-beta (Aβ) accumulation and tau neurofibrillary tangle formation. However, these features alone do not fully explain disease progression. Increasing evidence shows that chronic neuroinflammation serves as a major contributor to neuronal damage, but the interactions among the inflammatory pathways remain incompletely understood. Rather than evaluating each mechanism independently, this literature review examines how neuroinflammation, glial cells, the PI3K/AKT pathway, inflammasomes, SHIP-1, caspases, and genes and biomarkers interact to promote AD pathogenesis and evaluates their role in AD progression, which can eventually lead to an evaluation of their potential as biomarkers and therapeutic targets. The evidence indicates that microglial and astrocytic activation promote the release of inflammatory mediators, such as interleukins and cytokines. NLRP3 and NLRP1 inflammasome activation enhances caspase activity, cytokine maturation, pyroptosis, and tau formation. Furthermore, the dysregulation of the PI3K/Akt signaling pathway causes tau formation and amyloid beta plaque formation. Caspases additionally contribute to apoptosis, synaptic dysfunction, protein cleavage, autophagy, and more, exacerbating AD pathogenesis and neuroinflammation. Dysregulation of the SHIP-1 signalling pathway alters microglial activity and contributes to further neuroinflammation. Altogether, the findings of this review a model of AD pathogenesis involving interconnected inflammatory pathways rather than independent mechanisms. Understanding these interactions aids in identifying earlier inflammatory biomarkers and developing targeted therapies to intervene before severe AD.

Introduction

Alzheimer’s Disease (AD) is a progressive and irreversible neurodegenerative disorder that slowly destroys one’s memory and thinking skills. Although AD has traditionally been associated with amyloid-beta (Aβ) accumulation and tau neurofibrillary tangle formation, growing evidence shows that chronic neuroinflammation and its associated pathways are central contributors to the neuronal dysfunction that marks AD, making the currently accepted amyloid cascade hypothesis insufficient^[1]. Analyzing the dysregulated interactions between microglia, inflammasomes, and pro-inflammatory signalling pathways can allow scientists to accurately account for the pathogenesis of AD. This literature review delves deeper into the NLRP3 Inflammasome, NLRP1 Inflammasome, the SHIP-1 protein, caspases (Cas-1, 2, 4, and 9 in particular), the PI3K-Akt Pathway, and various genes and biomarkers associated with AD to provide a more holistic picture of the causes of Alzheimer’s. A better understanding of this topic could help create novel therapeutic targets and approaches to help treat patients. Additionally, identification of those biomarkers could aid in more personalized treatment approaches, highlighting the importance of expanding our understanding of AD pathology.

Methods

This literature review synthesized information from peer-reviewed and acclaimed scientific articles on the role of neuroinflammation and cell signalling (including, but not limited to: NLRP3, NLRP1, caspases, and SHIP-1) in AD. All the information was obtained from published literature found through scientific databases such as Google Scholar and PubMed. Search terms included combinations of “Alzheimer’s disease”, “neuroinflammation”, “inflammasome”, “NLRP3”, “NLRP1”, “caspases”, “SHIP-1”, and “neurodegeneration.” Reference lists from those relevant articles were also examined for additional studies. The inclusion criteria included studies relevant to AD, neuroinflammation, and neurodegeneration, and focused on studies published in English between 1999 and 2026. These papers included a mix of reviews as well as original papers in order to combine summaries of the field with evidence from individual experiments. To ensure that papers selected were relevant, papers on other neurodegenerative disorders (ex: Parkinson’s disease) were excluded.

Results

The results demonstrate that neuroinflammation is a key contributor to AD progression through interconnected glial, inflammatory, and signaling mechanisms. Through microglial activation, inflammatory processes and the subsequent release of pro-inflammatory mediators, there is significant oxidative stress, synaptic dysfunction, and impaired amyloid beta (Aβ) clearance, which leads to neuronal damage. This is exacerbated by the PI3K/Akt/mTOR pathway, which further promotes the Aβ accumulation and tau hyperphosphorylation, as it can cause neuronal death^[2]. The NLRP3 and NLRP1 inflammasomes, particularly connect Aβ- and tau-associated cellular stress to inflammation by activating caspase-1, IL-1β, IL-18, and pyroptosis^{[3][4][5]}. SHIP-1 also serves as an important regulator of PI3K/Akt signaling, NLRP3 activation, microglial reaction, lysosomal reaction, and more^[6]. The caspases, as aforementioned, play a significant role in neuroinflammation, as they cause pyroptosis and synaptic degradation as well as APP, Aβ, and tau exacerbations^[7]. These pathways are reflected by the genetic and molecular markers including APOE, TREM2, PSEN1, INPP5D/SHIP-1, Aβ, phosphorylated tau, TSPO, GFAP, ASC specks, and inflammatory cytokines^[8]. Therefore, these findings demonstrate that AD progression is caused by a reinforcing network of microglia, astrocytes, inflammasomes, caspase activity, signalling dysregulation, and Aβ and tau pathology.

Discussion

The findings of this review support the novel model proposed in this paper in which chronic neuroinflammation serves as an interconnected and self-reinforcing network that contributes to disease progression. This synthesis builds on various existing studies by connecting mechanisms. Interactions among the microglia, astrocytes, inflammasomes, caspases, SHIP-1, and PI3K/Akt signaling show the convergence between inflammation and mechanisms of AD progression. The microglia and astrocytes, the glial cells that serve to maintain homeostasis in the brain, can cause neuroinflammation and neurodegeneration by producing inflammatory mediators. Inflammasomes recruit and activate inflammatory caspases and further tau deposition, exacerbating AD. Following that, caspases can cause apoptosis and many effects that ultimately lead to worsening neuroinflammation and tau protein deposition. SHIP-1 signalling also contributes, as it influences neuroinflammation and alters the brain's ability to clear amyloid plaques. Similarly, PI3K/Akt signalling causes hyperphosphorylation and excess autophagy. Lastly, the biomarkers and genes that are predictive of AD contribute to pathogenesis by causing various changes in protein production. The dysregulation of these essential pathways promotes the Aβ-tau cascade, pyroptosis, synaptic dysfunction, and greater neuronal loss. Considering these mechanisms together provides insight into AD pathogenesis

Conclusion

Therefore, this interconnected model presented in this paper can explain the pathogenesis and progression of AD. The importance of these pathways is highlighted by their implications for earlier detection and therapeutic intervention. Profiles incorporating indicators of glial activation, inflammasome activity, caspase signalling, and inflammatory mediators may be more informative due to the variability of AD. Future studies should therefore determine whether specific combinations of inflammatory biomarkers can distinguish inflammatory subtypes or disease stages and whether the presence of biomarkers can indicate disease prior to significant neuronal loss. Additionally, there are limitations to consider. First, some of the mechanistic evidence is from transgenic mouse models, which cannot fully represent the complexity of human AD. Second, the pathways examined in the review have been investigated with different methodological approaches, which limits direct comparison across studies. Finally, as this review synthesizes selected literature, it cannot quantitatively determine the exact contribution of each pathway to AD progression. Future research should prioritize longitudinal human studies to observe the temporal sequence of inflammatory changes relative to current knowledge of AD progression markers, such as Aβ accumulation, tau pathology, neuronal loss, and cognitive decline.

References

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