Effects of Microglial Interleukin-1β in the Pathophysiology of Alzheimer's disease

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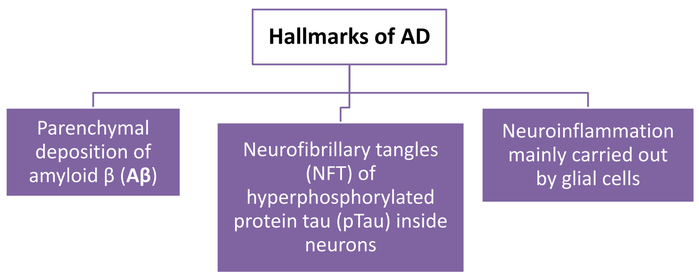
Introduction

• **Alzheimer's Disease (AD)** is a neurodegenerative disorder characterized by loss of cognitive function, representing the most common cause of dementia in the elderly.



• Aβ is formed by secretase cleavage from its precursor (APP). Its accumulation is supposed to trigger the other events in AD.

• Glial response to Aβ could lead to:
  • A pro-inflammatory state, detrimental for the disease
  • Struggle to maintain brain homeostasis

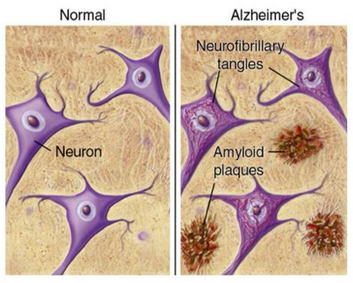


Fig 1. Hallmarks of AD[1]

• The aim of this work is to carry out a review in which:

1. Microglial activation towards Aβ is studied
2. Effects of pro-inflammmatory interleukin-1β (IL-1β) are reviewed
3. Treatments targeting neuroinflammation are mentioned

Methods

• **Scientific literature search on PubMed database:** using as keywords *Microglia + Alzheimer's Disease + IL-1β* or derived combinations. Articles cited in articles or reviews were also consulted. Papers were sorted by relevance.

Results

1. Microglial response to Aβ

• Microglia are essential glial cells for brain homeostasis. They can be found around Aβ (Fig 2) and are able to recognize and phagocyte it. The exact receptors involved in the process are still in debate.

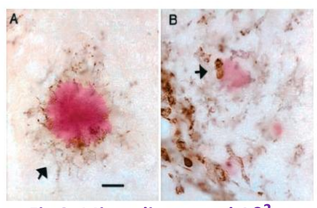
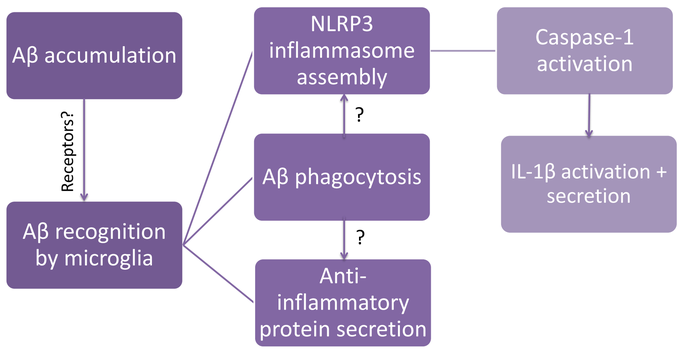


Fig 2. Microglia around Aβ[2]

• They can have different activated phenotypes, being able to secrete both anti- and pro- inflammatory proteins (such as IL-1β) depending on the context. Mechanisms driving each type of activation are poorly understood.

• The NOD-, LRR- and pyrin domain-containing 3 (NLRP3) inflammasome is required for caspase-1 activation, which leads to maturation of pro-IL-1β to IL-1β. It can be assembled in microglia after exposure to Aβ, but the precise mechanisms are also still discussed.



Results

2. IL-1β effects

On Aβ burden

• First studies *in vitro* supported that IL-1β increased Aβ accumulation and was detrimental for the disease.

• *In vivo* mice models of IL-1β overexpression (Fig. 3) showed that IL-1β decreased Aβ burden. Blocking its expression increased Aβ: thus, they support a more physiolgycal role of the cytokine.

• IL-1β can increase the expression of certain chemokines, which can recruit inflammatory cells from the periphery into the brain. Some of those cells contribute to Aβ clearance by phagocytosis.

• It has been also proposed that IL-1β could decrease Aβ burden in the brain by increasing the activity of non-amyloidogenic secretases (α-secretase family). However, the effects found are very variable between cell lines.

Reported effects of IL-1β on secretases* of different cell lines

Rat Primary Cortical Neurons	α-secretase ↑ APP levels unchanged
Neuroblastoma SK-N-SH + Mouse Primary Cortical Neurons	α-secretase ↑ APP levels unchanged
Neuroglioma U251	α-secretase ↑ APP levels ↓
HEK293 cells	γ-secretase ↑ Aβ ↑

* α-secretase precludes Aβ formation; while γ-secretase participates in both non- and amyloidogenic APP processing

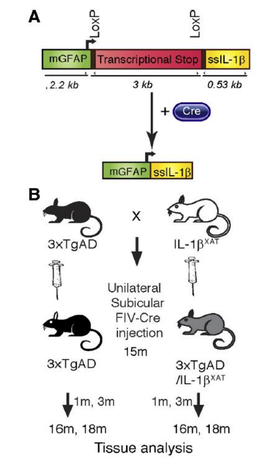


Fig 3. Mice model of IL-1β overexpression[3]

Others

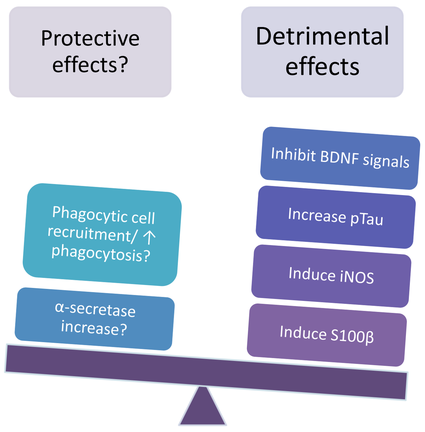
• Besides its debatable role in Aβ accumulation, IL-1β has other effects that could increase neurodegeneration.

• IL-1β can inhibit Brain Derived Neurotrophic Factor (BDNF) signaling, impairing spine formation and synaptic plasticity.

• It can also activate kinases that will phosphorylate protein tau. This precedes formation of NFT and neuronal dysfunction.

• Moreover, it can increase inducible Nitric Oxide Synthase (iNOS) levels, enhancing Nitric Oxide production. This also increases oxidative stress, propitiating neurotoxicity.

• In addition, it can induce S100β production in astrocytes. This protein can further increase NFT formation, neurodegeneration and oxidative stress.



• Finally, it can activate its own expression, creating a neurodegenerative cycle, as summarized in the scheme (Fig 4).

Schematic overview of IL-1β triggered pathways

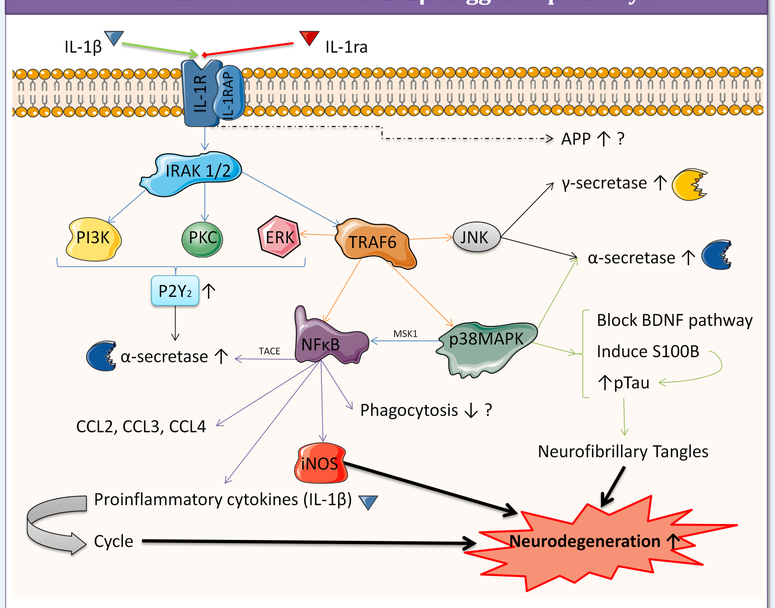
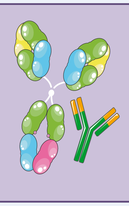


Fig 4. Upon binding to its receptor, IL-1β triggers the activation of several pathways that can lead to an increase in neurodegeneration via diverse mechanisms[4]

3. Treatment approaches

• Peptides that shift microglial activation towards an anti-inflammatory are being studied.

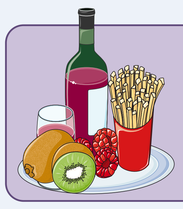
• Treatment with non-steroidal anti-inflammatory drugs has also been tried, but was less effective than expected.



• Anti-IL-R antibodies decreased IL-1β signaling and improved cognitive behavior in AD mice models.

• Aβ immunization showed similar results.

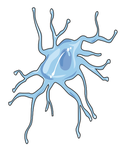
• Application in patients is controversial due to possible side effects.



• Calorie restriction (CR) in rats has been shown to decrease IL-1β levels and improve cognitive deficits.

• CR can also decrease pro-inflammatory cytokines in AD mice models, and to reduce the levels of pTau.

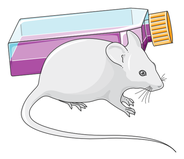
Conclusions



• Glial cells are actively implicated in the pathogenesis of AD. Precise mechanisms are still unclear, but it is by now accepted that microglia becomes activated after Aβ exposition. They can both phagocyte it and secrete proinflammatory proteins in response.

• Initial function of IL-1β is still in debate whilst other, negative effects for AD pathogenesis are in a more general agreement.

• Consensus is needed in the models used: when carried out in different models and IL-1β treatment conditions, studies generate controversial results. Drawing conclusions would be easier if studies were carried out in equal conditions and results were reproduced.



• More *in vivo* experiments are lacking to deeply study if IL-1β effects, where involvement of other cytokines may interfere.

• New treatments trying to reduce overall neuroinflammation are being studied. Translation into applications for real patients must be regarded carefully due to possible adverse effects.

References

1. *© 2000 BrightFocus Foundation*
2. Wilcock DM, DiCarlo G, Henderson D, Jackson J, Clarke K, Ugen KE, et al. Intracranially administered anti-Abeta antibodies reduce beta-amyloid deposition by mechanisms both independent of and associated with microglial activation. J Neurosci. 2003;23(9):3745–51.
3. Ghosh S, Wu MD, Shaftel SS, Kyrkanides S, LaFerla FM, Olschowka J a, et al. Sustained interleukin-1β overexpression exacerbates tau pathology despite reduced amyloid burden in an Alzheimer's mouse model. J Neurosci. 2013;33(11):5053–64.
4. Scheme made by the author.