Microglia and the fight against Amyloid β in late-onset Alzheimer's Disease.

Microglia and their task of detecting, clearing, and adjusting to amyloidosis

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Table of Contents

1 Abstract

Alzheimer's disease is the leading cause of dementia, with late-onset Alzheimer's disease (LOAD) accounting for the majority of cases. A key feature of the disease is the build-up of amyloid-β (Aβ) plaques in the brain, which contributes to cognitive decline. Microglia, the brain's primary immune cells, play a central role in responding to these plaques. They work by identifying and clearing Aβ through a process called phagocytosis. Their function is guided by several surface receptors, including TLR2 (Toll-like receptor 2) and TAM (Gas6/Tyro3-Axl-Mer receptors) receptors (Axl and Mer), which help them recognize and remove harmful substances. However, when overactivated, these responses can become harmful, contributing to ongoing inflammation and damage.

Recent research shows that microglia are more complex than once thought. Rather than falling neatly into "good" (anti-inflammatory) or "bad" (pro-inflammatory) categories, like previously believed, microglia show a wide range of states that change depending on the environment and disease stage. One important discovery is the presence of disease-associated microglia (DAMs), which become activated in response to Aβ plaques. This shift in state is regulated by genes such as TREM2 and APOE, which are known to influence the risk of developing Alzheimer's. These genetic risk factors can affect how well microglia respond to damage and clear plaques, making them important targets for future research and therapy.

Ultimately, the thesis underscores the need for deeper insights into microglial biology and disease staging to develop targeted interventions. A more nuanced understanding of microglial heterogeneity and their interactions with pathological hallmarks may unlock novel avenues for early diagnosis and therapeutic modulation in Alzheimer's disease.

2 Introduction

Alzheimer's is the most common cause of dementia worldwide, causing 60-70% of all instances ("2025 Alzheimer's Disease Facts and Figures," 2025). In reports from 2025, it was estimated that it affected 7.2 million Americans, of whom 7 million were above the age of 65 ("2025 Alzheimer's Disease Facts and Figures," 2025). It is a rather slowly progressing disease, which starts with the loss of short-term memory, and later can develop into speech impairment, long-term dementia, disorientation, and psychological symptoms like self-neglect and isolating behaviour. (Maccioni et al., 2018; McGeer, 2001)

Better prevention methods and more aggressive treatment of lifestyle-related risk factors, for example, hypertension, cardiac health issues, and hypercholesterolemia, seem to lower the relative chance of developing AD (Eikelenboom et al., 2012; Wilson et al., 2011; Langa, 2015). Still, as the total life expectancy keeps rising and population pyramids project high numbers of elderly by the year 2040, total numbers have already dramatically risen in the past 10 years, from 5.1 to 7.2 million, and will most probably keep on rising (Hebert et al., 2013; "2025 Alzheimer's Disease Facts and Figures," 2025, "2015 Alzheimer's Disease Facts and Figures," 2015). It was estimated that due to both this aging baby boom generation and unhealthy lifestyles, numbers in the US might increase by more than 10 million cases (Weuve et al., 2014; Wilson et al., 2011).

The disease is very multifaceted, with a large array of complications and alterations linked to it. However, the parameter changes are different among individuals, thus making it hard to determine a common villain in the story (Serrano-Pozo et al., 2011).

Microglia have tentatively been linked to AD. These cells are the intrinsic immunological mediators in the brain, being involved in the production and reception of many chemokines and cytokines. They can either be in a resting state or an activated one, through both exterior signals, such as inflammatory signals from the periphery, and CNS-derived signals, like lesions, infections, or compounds indicative of pathology (Färber & Kettenmann, 2005; Saijo & Glass, 2011).

A large body of research has appointed innate immunity as the main culprit in disease pathology. One theory on the matter, put forth by Maccioni and colleagues, states that microglial activation alters microglia-neuron communication and may initiate pathological cascades in response to damage signals, subsequently promoting tau protein hyperphosphorylation and oligomerization, initiating a positive feedback loop characterizing itself in neurodegeneration. Yet, they also recognise that it might not be the main initiator of the disease, but rather a driver in the deterioration, early on in disease development (Maccioni et al., 2018).

To add to this, many genetic mutations or predispositions for microglial cells have been correlated with both late- and early-onset Alzheimer's, the latter will not be touched upon in this thesis, however it is recommended to read through a great review by Mendez (2019) on all it's known variants (Mendez, 2019). Many of these mutations influence both activation of and totalling numbers of microglia in turn causing neurotoxicity, more on that later in this review (Block et al., 2006).

This thesis aims to highlight microglia and their task of detecting, pacifying, and the risks of losing to Amyloid-β will be explored. Focusing on recent changes in interest in the innate immune cells and trying to answer the question of how they go about their fight against amyloid plaques and fibrils, and where issues can arise. While also exploring their usefulness as a possible therapeutic or diagnostic tool in the future.

3 Chapters

3.1 Microglia functionality and detection of Aβ

Microglial cells are the unique macrophages of the central nervous system. They regulate homeostasis, neuroinflammatory markers, and neurogenesis among other things. Thus, in turn, are also part of neuropathological pathways, for example, in neurodegenerative diseases like Alzheimer's (Lannes et al., 2017; Gao et al., 2023; Kinghorn et al., 2020). Resting microglia create a fast network of ready-to-go state cells that actively monitor the CNS and act where needed. They phagocytose misfolded proteins, cellular debris, or dying cells. They also provide cytokines and other signalling molecules to recruit other immune cells or promote neurogenesis and brain development (Gao et al., 2023; Kinghorn et al., 2020). They additionally communicate directly with neurons using specialised connections (Cserép et al., 2019). Previously, the cells had been shipped with a homogeneous function. However, new technologies reveal that individual differences in single cell expression and or function exist, and clusters are formed of those functioning similarly. Showing that microglia are highly heterogeneous (Lannes et al., 2017; Gao et al., 2023).

Microglial cells have a plethora of functions, differing throughout multiple stages of development (Galatro et al., 2017). In the early stages of brain development, microglial levels are relatively low and increase with age (Galatro et al., 2017). While the brain is still developing, it functions to limit excessive neuron formation, clean up apoptotic cells, support neurogenesis and neuron migration, and promote angiogenesis and synaptogenesis, with more functionalities still being discovered (Lannes et al., 2017; Salter & Beggs, 2014). Neuron pruning issues have been connected to autism spectrum disorders, whereas immune-related deformations have been linked to neurodegenerative diseases (Spittau, 2017). Later in life, they take on a more protective and phagocytic role as well

Traditionally, microglial subtypes or classes were divided into M1 or pro-inflammatory cells and M2 or anti-inflammatory cells (Heneka et al., 2014; Mishra et al., 2012). This classification is, however, outdated, and more recent research has shown that microglia show a more continuous spectrum of phenotypes (Heneka et al., 2014; Ransohoff, 2016). Recent discussions on the matter have led to the redefinition of both how microglia get classified and on what metrics these classifications can be based. Due to the complicated expression of functional genes, intra- and extracellular markers, and morphology, groupings are difficult to establish. Especially, considering local reactivity and the environment to whose signals microglia individually react, whether pathological or not.

All these limitations of the oversimplified and flawed M1-and-M2-system have been beautifully laid out in a publication by Paolocelli et al. (2018) (Figure 2). In this overview, they gathered a multitude of experts in the field and gave them a survey on what they currently use, agree with, and disagree with regarding nomenclature. The conclusion was drawn that there is a lack of a proper naming and division system as of now. However, it was universally agreed that the spectrum of microglia was non-dichotomous, rather extremely intricate and highly variable in all depths of complexity, as shown in Figure 1. More recent

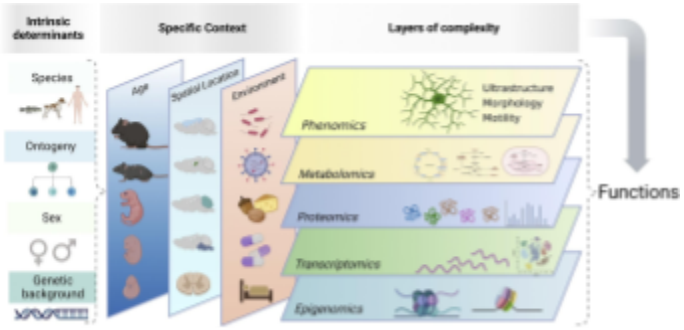

Figure 1: Layers of complexity regarding microglial nomenclature
Layers of complexity and or affecting factors for typing are shown in the schematic of Figure 1A. Showing the importance of not only location of origin and other context, but also in what levels the cells may differ, with all forms of variables listed in the layers of complexity.

papers have begun to refer to microglial 'subtypes' as states. Current nomenclature is signature-based in an effort not to oversimplify the intricacies too much.

Microglia are highly plastic between most states and have been found to return to 'homeostatic' levels shortly after the specialised needs are met, excluding some that seem to be more permanent in most cases.

For the surveillance of their direct surroundings, microglia use a large assortment of surface receptors. Toll-like receptors are one of the most abundant groups of mostly extracellular receptors, with exceptions for TLR3, TLR7, and TLR9, which are presented intracellularly (Fiebich et al., 2018; Akira, 2010). They mediate innate immune responses, especially but not limited to, in the CNS. TLRs respond to certain pathogen-associated molecular patterns (PAMPs), like LPS (Lipo-polysaccharides) or bodily signals of inflammation, for example (Li et al., 2013). They depend on dimerization of receptors, initiating a cascade resulting in the translocation of nuclear factor kappa B (NF-kB), mediating the production of pro-inflammatory signals, like cytokines (Fiebich et al., 2018; Akira, 2010). The dimerization is facilitated by proteins like MyD88, except for TLR3 (Akira, 2010). Microglia express all receptors within the family; however, expression is only mediated near the circumventricular organs, where there is direct access and interaction with the bloodstream (Olson & Miller, 2004). Within the family, TLR2 has been subjected to the most neurodegenerative research.TLR2 needs to bind CD14 to activate the phagocytic process of Aβ proteins (Reed-Geaghan et al., 2009). TLR2 activation led to an increase in the uptake and phagocytosis of pathological Aβ proteins in a somewhat older report (Chen et al., 2005). But, in more recent research, the contrary has been shown. In studies using TLR2 knockout mice and others where TLR2 was inhibited, mice showed better clearance of plaques and less cognitive decline (McDonald et al., 2016; Jana et al., 2008; Lin et al., 2012; Liu et al., 2013). It is hypothesized that the overactivation of TLR2 led to an impairment of Aβ clearance, but more on that later.

However, TLRs do not seem to be the main receptors tied to the phagocytosis of toxic Aβ deposits. That title goes to the TAM-receptors Axl and Mer, already proven to be important in the process of engulfing dead cells in the CNS (Fourgeaud et al., 2016; Lemke, 2013). In a study by Huang et al. (2021),

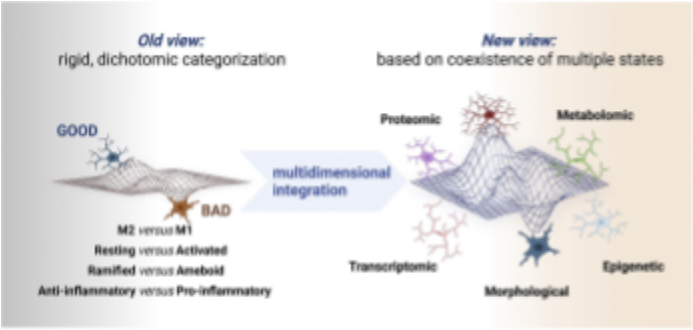

Figure 2: Schematic of microglial complexity and spectrum
In Figure 1B, the dichotomous old view is shown on the left, having two peaks for either good or bad microglia. The new view on the right shows highly differing peaks, influence of varying markers leading to highly diverse arrangement of microglial states. Schematics taken from Paolicelli et al. (2022) and then compounded.

they followed up on the previously established critical role of these receptor tyrosine kinases (RTKs) by looking at their role in the clearance and uptake of Aβ plaques. They found an upregulation of Axl, a normally relatively sparsely expressed receptor in homeostatic conditions, with the start of plaque formation in APP/PS1 mice, a well-known AD mouse model. Interestingly, this increase was only found in plaque-associated microglia, hinting that the presence of amyloidosis leads to the expression of the genes. The RTKs respond to their respective ligand, Gas6, which was found to be heavily upregulated in plaques. When using Axl- crossbreeds of the mouse model, this increase was not found, indicating that the expression of Axl led to an increase in plaque-associated Gas6 and thus receptor activity (Huang et al., 2021). This correlated with previous research elaborating on the Axl-dependence of Gas6 transcription (Zagórska et al., 2014; Huang et al., 2021).

Furthermore, they found that the microglia RTKs interact with plaques directly initiating phagocytic mechanisms. This showed the detection of, engagement with, and reaction to the amyloid plaques. Shown through the usage of mutations negative for both receptors, the relative distance, and interactions of their microglia with Aβ proteins. They further proved the necessity of TAM-receptors for phagocytosis of plaques (Huang et al., 2021).

3.2 Alzheimer's pathologies

3.2.1 Amyloid-β plaque pathology

Alzheimer's disease (AD) is defined by two principal hallmark features: amyloid-β (Aβ) plaque formation and tau protein aggregation into neurofibrillary tangles (Lannfelt et al., 2014). According to the amyloid cascade hypothesis, the pathological process begins with the cleavage of amyloid precursor protein (APP). It ends with the creation of Aβ peptides (38–43 amino acids) (Hardy & Higgins, 1992). In pathology, these peptides aggregate into soluble plaques, then fibrils, and eventually into insoluble plaques primarily of the 40- and 42-chain variants (Haass & Selkoe, 2007; Lannfelt et al., 2014). In physiological conditions, they would be cleaned up by microglial phagocytosis using APOE binding and repurposed (Lannfelt et al., 2014).

The process of producing these toxic Aβ has been widely researched over the years. APP can be processed in two different ways, amyloidogenic (right side in Figure 3) and non-amyloidogenic (left side in Figure 3) (Chen et al., 2017). The latter involves the initial cleavage of APP using α-secretase, producing membrane-bound α-C terminal fragments (CTF). The clipped and cleaved sAPPα is released, the production of sAPPα can be increased after ACTH receptor activation and or an electrical stimulus, hinting that neural stimulus increases usage of the α-secretase pathway for cleaving APP. The CTFα gets cleaved by

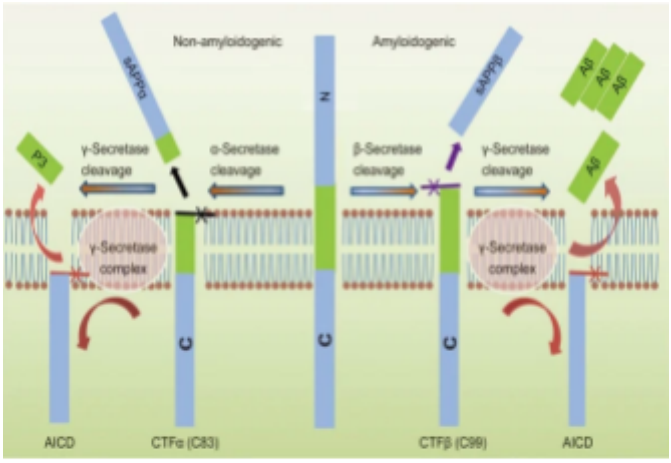

Figure 3: Cleavage of APP:
The schematic shows the two ways a bound APP can be cleaved (left: non-amyloidogenic, right: amyloidogenic). Bound APP is cleaved by either α- or β-secretase, the prior creating CTFα (C83) and sAPPα, the latter creating CTFβ (C99) and sAPPβ. CTFα gets further processed into the APP intracellular domain (AICD) and P3 by γ-secretase. Whereas the same γ-secretase produces varying Amyloid β lengths ranging from 38-43 amino-acids long from CTFβ, leaving the remaining AICD as well. Figure made and displayed by Chen et al. (2017).

γ-secretase, liberating the P3-lipid from the membrane and leaving a so-called APP intracellular domain (AICD). For an amyloidogenic cleavage, APP is first cleaved by β-secretase, producing a CTFβ and releasing

sAPPβ. After producing the CTF, it can be either kept external, cleaved by γ-secretases leading to less toxic lengths of Aβ protein (38, 39, 41, and 43), or the complex gets internalized and cleaved by γ-secretase, producing Aβ-40 and Aβ-42 proteins (Chen et al., 2017).

Despite all this, clinical trials targeting Aβ clearance have largely failed to find cognitive benefits, even with significantly lower plaque occurrence. This has raised questions on whether Aβ-plaques are a viable therapeutic target, and suggests other pathological processes are involved in the cognitive impairment of AD patients (Lannfelt et al., 2014; Panza et al., 2014). The initiation of pathology, however, is hypothesized to be primarily amyloidosis-based (Chen et al., 2017).

3.2.2 Tau pathology

Tau pathology is the hyperphosphorylation and aggregation of tau protein, which under regular conditions, supports cytoskeletal stability and neuronal function (Wang & Mandelkow, 2015; Price & Morris, 2004). Modifications, like protein misfolding, cause tau pathology. The proteins dissociate from the microtubules, leading to synaptic loss and the formation of neurofibrillary tangles (Wang & Mandelkow, 2015). Previously, it was thought that tauopathy was spread between neurons through tau "seeds" that induce neighbouring proteins to also misfold and aggregate; however, more recent research hinted that the culprit of spreading these seeds might be microglia (Maphis et al., 2015; Hopp et al., 2018). Studies on the matter have not found microglia to actively distribute them, but they did find that microglia are incapable of properly neutralizing the toxic proteins (Hopp et al., 2018). This then leads to their neurodegeneration and or the release of still "seeding" proteins into the interstitial space (Hopp et al., 2018). Tau pathology correlates quite closely with cognitive decline, closer than Aβ-pathology does. Hinting at it having a more direct role as mediator of dementia and related symptoms (Johnson et al., 2015).

3.3 Alzheimer's, Microglia, and the fight against plaque formation

3.3.1 Damage/Disease-associated Microglia

Neuroinflammation is a response within the CNS triggered by an infection, trauma, toxins, or ischemia. The response is mediated by the resident microglia and astrocytes, along with infiltrating monocytes and the endothelial cells of the capillary (DiSabato et al., 2016).

Initially in AD, later also in other neurodegenerative diseases, transcriptomics in mouse models revealed a transition into disease-associated microglia (DAMs), protective hyper-activated microglia to combat protein-specific deposits (Friedman et al., 2018; Keren-Shaul et al., 2017). Keren-Shaul et al. (2017) provided insight into these distinct microglial states through single-cell RNA sequencing (scRNA-seq). They sorted all the immune cells (CD45+) in the brains of both a 5XFAD (AD-mouse model) and a wild-type control group. They sequenced and created distinct subclusters based on gene expression levels. Three microglial clusters were created, two of which seemed to be developed into a new state: pro-inflammatory, upregulation of APOE (Apoliprotein E), Lpl (Lipoprotein lipase), Cst7 (Cystatin F), TREM2 (Triggering receptor expressed on myeloid cells 2), among many more, termed DAMs (Keren-Shaul et al., 2017). They followed up this research, using a different marker (CD11C+) for sorting the immune cells to see if any other marker than CD45+ could be indicative of AD progression (Keren-Shaul et al., 2017). The CD11C+ sorting led to a 6.3-fold increase in relative DAM abundance in the sorted sample (Keren-Shaul et al., 2017). The CD11C+ marker is, however, heterogeneous over multiple different immune cells, probably lowering biological relevance (Keren-Shaul et al., 2017).

Next to sorting differently, they also kept track of microglial transition into DAMs, tracking clustering over 8 months with measurements at 1, 3, 6, and 8 months, shown in a kNN (K-Nearest Neighbour) graph, which indicates how similar expression levels are based on distance between two points (Figure 4) (Keren-Shaul et al., 2017). They revealed an intermediate transition state between regular inhibited (homeostatic) microglia and DAMs (Keren-Shaul et al., 2017). This data, model, and methodology have since been replicated in humans with similar results. Highlighting that the mouse model is very well-suited as a testing ground for understanding Alzheimer's and microglial interaction (Friedman et al., 2018).

The intermediate stage is also referred to as stage 1, and the transition of homeostatic microglia into stage 1 was shown to be TREM2-independent, whereas further transition into a DAM is dependent on TREM2 (Friedman et al., 2018; Keren-Shaul et al., 2017). TREM2, another one of the upregulated genes in DAMs, forms a signalling complex with Tyrobp (Tyro protein tyrosine kinase binding protein) (Keren-Shaul et al., 2017; Friedman et al., 2018). These two genes are important for the signalling regarding phagocytosis and lipid metabolism in the brain (Basha et al., 2023; Keren-Shaul et al., 2017). Canonically, this cascade involved Tyrobp as the coupled protein, initiating further intracellular gene regulation through spleen tyrosine kinase (SYK) (Basha et al., 2023). Initiation of this pathway with APOE is necessary for the differentiation into DAMs (Basha et al., 2023; Keren-Shaul et al., 2017). The prevalence of this transition is enforced by the inhibition of regulatory signals, like Cx3cr1, P2ry12/P2ry13, and others (Gu et al., 2015;

Reshef et al., 2017; Keren-Shaul et al., 2017; Butovsky et al., 2015; Hickman et al., 2013; Merino et al.,

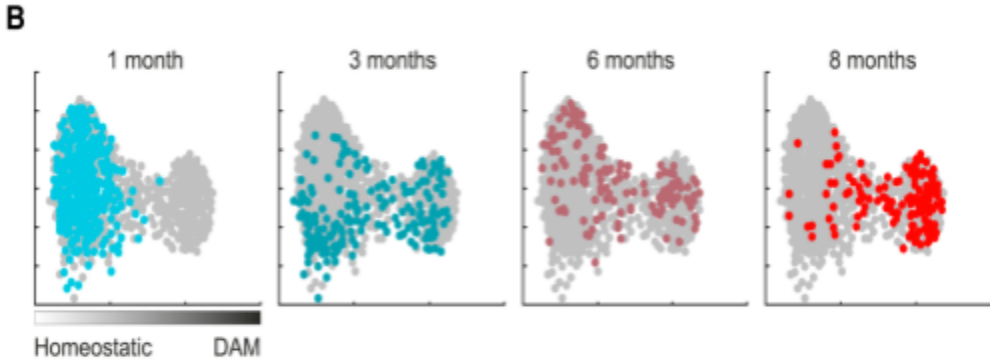

Figure 4: Transition from homeostatic microglia to DAM
kNN (K-Nearest Neighbour) projection of the cells taken from the AD mouse at each time point along disease progression (1, 3, 6, 8 months). Gray refers to all data points. X-axis refers to the transition axis from homeostatic microglia to DAM. Distance between points shows similarity in expression profile, closer is more similar). This shows the transition of most cells into disease fighting hyperactive DAMs over the period of disease. Graph courtesy of Keren-Shaul et al. (2017)

2016). Cx3cr1 modulates spine pruning and nerve health, whereas P2ry12/P2ry13 regulate the neurogenesis and repair of injured neurons (Gu et al., 2015; Reshef et al., 2017). By inhibiting genes that promote neuron health and regulation, microglia lose most of their repairing function, which allows the cells to focus on fighting infections or pathogenesis (Keren-Shaul et al., 2017).

After transition into stage 2, or a DAM, microglia focus mostly on the inhibition of pathology by upregulating other genes involved in the clean-up of effectors and differentiation mediating molecules, e.g., the APOE, Lpl, Cst7, and TREM2. After conversion and fighting the pathology, these ex-DAMs tend to normalize their gene expression back to homeostatic levels. However, they do not seem to recover to healthy pre-pathology microglia fully. It is unknown whether this is a priming mechanism for future reactivity or whether it is a sign of exhaustion of the cell (Lan et al., 2024; Deczkowska, 2024). In a study on neonatal SPP1+-EGFP mice that had an induced stroke, which prompted the microglial transformation into DAMs (Lan et al., 2024). After the stroke, a lot of the ex-DAMs transitioned back into regular microglial cells, but reintroduction of pathology led to a quicker response, highlighting a memory-like function (Lan et al., 2024). In contrast, juvenile and adult mice found themselves getting rid of ex-DAMs, plausibly showing the irreversible nature of DAM transition (Lan et al., 2024).

3.3.2 Genetic predisposition for LOAD through microglial dysfunction

Late-onset Alzheimer's disease (LOAD) is often sporadic in showing its symptoms. However, a lot of research has been put into finding risk factor genes for the development of this neurodegenerative disease

(Durmaz et al., 2019). As much as 70% of the disease risk is thought to be caused by genetic predispositions (Vilatela et al., 2012). Most of these cases include the rare early-onset or familial Alzheimer's disease; however, those are beyond the scope of this review (Vilatela et al., 2012; Durmaz et al., 2019).

A major risk gene for LOAD is the APOE gene, and specifically one of its polymorphisms. The gene consists of three polymorphic alleles ε2, ε3, and ε4 (Bu, 2009). In a genotype assay by Durmaz et al. (2019), the presence of a single ε4 allele for the gene (*APOE*4 (+)) was found to increase the risk of LOAD by 4.4 times (Durmaz et al., 2019).

This protein is thought to be the primary lipid transporter in the brain among many things (Uddin et al., 2018). It is expressed both in the periphery and the CNS (Raulin et al., 2022). produced mainly by the liver in the periphery and helps with both low-density lipids (LDL) and high-density lipids (HDL) transport, the latter its source of synthesis is primarily the astrocytes in the Blood-Brain-Barrier (BBB) and microglia (Raulin et al., 2022; Uddin et al., 2018). The influence of peripheral APOE on neurodegenerative diseases could be different than that of the brain-derived counterpart, and should thus be treated and researched differently, but that is beyond the scope of this thesis. Furthermore, the functionality and intricacies of APOE4 negatively affect a plethora of systems, all of which are shown to be influential in AD pathology. In this thesis, the most mentioned and main alterations of the APOE allele are discussed, for a deeper understanding; a great review by Kanekiyo et al. (2014) goes into many of the varying relations among the ones mentioned here.

The three isoforms of the protein are only altered by single amino acids, but these seemingly small changes alter the protein's structure and binding affinity to receptors. Extracellularly, the proteins bind to lipids in the interstitial space, transporting them to surface-level receptors for endocytosis. Intracellularly, the proteins influence a multitude of cellular processes, including the speed of endocytosis of APP by LRP1 (low-density lipoprotein receptor-1) receptors (Zerbinatti et al., 2004). LRP1 receptors have a wide range of binding agents, including both APP and APOE. The speed of endocytosis influences the extent to which the toxic Aβ proteins are produced (Bu, 2009; Zerbinatti et al., 2004). Although most Aβ peptides are secreted to the extracellular space, some can aggregate in the late endosomes or lysosomes and contribute to intraneuronal Aβ accumulation. This can lead to apoptosis, releasing an abundance of Aβ deposits in its vicinity (Bu, 2009; Zerbinatti et al., 2004).

Moreover, the formation or clearance of Aβ plaques is affected by the isoform APOE alleles differently (Castellano et al., 2011). In a study looking at CSF free fluid Aβ, researchers found a lower level of free Aβ in individuals with the protective allele types compared to ε4 counterparts, later detecting high amounts of deposits not flushed out of the brain, left there in malicious plaques (Castellano et al., 2011). They further investigated the clearance levels of these individuals, finding that the ε4 allele affected clearance negatively (Castellano et al., 2011). Other studies found that APOE4 binds worse to Aβ and that these complexes are degraded at a slower rate than APOE3-Aβ and APOE2-Aβ complexes (LaDu et al., 1995; Deane et al., 2008). These results indicate a wide variety of risks associated with the more risk-prone APOE4 isoform. However, plenty more studies have come out recently with more and more systems affected or influenced by the deleterious allele.

TREM2, another major risk gene for LOAD, as previously highlighted, forms a signalling cascade with Tyrobp, also known as DAP12 (DNAX-activating protein 12) (Basha et al., 2023). Rare genetic variants of the TREM2 can lower the effectiveness of the receptor, lowering binding efficacy and activity of induced responses. TREM2 expression in microglia is based on the sensing of apoptotic cells and lipids (Basha et al., 2023). In a series of studies on the effect of TREM2 on Aβ clearance and microglial motility, it was found that individuals without proper TREM2 expression had many more plaques, took longer to metabolize the pathogenic Aβ, and could not be saved by the inhibition of CD33 (Griciuc et al., 2019; Gratuze et al., 2018). CD33 is a downstream signalling receptor that is inhibited by TREM2 (Griciuc et al., 2019). In vitro overexpression of CD33 without TREM2 leads to higher amounts of plaques in 5xFAD mouse models, but the reintroduction of TREM2 recovered some of the damage done to the brain, whereas the opposite was not found to be true, indicating that TREM2 affects transcription for CD33 (Gratuze et al., 2018). TREM2 variants R47H and T96K both cause ligand-binding defects; they additionally show a higher mortality rate among AD patients and faster death after diagnosis (Dijkstra et al., 2025; Gratuze et al., 2018). The role of TREM2 in AD progression in general is still incompletely understood. However, strong data on microglial expression levels, inhibition factors, variants, and a better understanding of the mechanistic workings indicate that TREM2, when normally expressed and functioning, is beneficial for AD, but when less effective at binding or overproduced, can negatively impact microglia in fighting the disease (Dijkstra et al., 2025).

CD33 itself is part of a group of receptors called sialic acid-binding immunoglobulin-type lectins (SIGLECs) (Schwarz et al., 2014). The receptor group consists both of CD33-related receptors (CD33, SIGLEC5-12, 14, and 16) and 4 others (SIGLEC1, SIGLEC2, SIGLEC4, and SIGLEC15) (Estus et al., 2019). CD33-related receptors are the primary SIGLECs expressed in microglia (Zhang et al., 2015). These receptors are poorly conserved and seem to evolve rapidly compared to receptors of other groups (Schwarz et al., 2014). As indicated by their name, SIGLEC receptors mainly bind to sialic acid. Both sialic acid and SIGLEC receptors seem to be in abundance in Aβ-plaques, among other pathophysiological hallmarks (Salminen & Kaarniranta, 2009). All but SIGLEC14 and -16 in the CD33-related receptor subfamily express a domain called immunoreceptor tyrosine-based inhibitory motif (ITIM)(Schwarz et al., 2014). This motif initiates a cascade that leads to an eventual reduction in CD33 presence by stimulating the production of E3 ligases that break down CD33 receptors (Walter et al., 2007). Another result of this cascade is an overall decrease in immune cell activation and Aβ clearance (Hernández-Caselles et al., 2005). In recent years, genome-wide association studies (GWAS) have revealed some SNPs significantly linked to a reduction of AD risk (Jansen et al., 2019). Rs3865444, a SNP that led to the production of some CD33 receptors missing the second exon, termed D2-CD33 (Malik et al., 2013). In follow-up studies, it was hypothesized that this version of the receptor cannot bind sialic acid, and has an ITAM-like, rather than an ITIM, signalling cascade, initiating the same pathway as TREM2, inducing phagocytic activity in microglia (Malik et al., 2013; Keren-Shaul et al., 2017; Underhill & Goodridge, 2007). A reduction of CD33 using a different SNP did not affect plaque clearance; however, the induction of D2-CD33 transcription did affect clearance positively (Bradshaw et al., 2013). Showing that D2-CD33 impacts AD risk by initiating microglia to transform into DAM-like states, like TREM2 (Estus et al., 2019).

3.3.2 Systemic inflammation

Although genetic predisposition increases baseline risk for the pathogenesis of AD. As a multi-faceted disease, a lot of other physiological alterations can massively increase the chance of developing AD. One of the most researched external risk factors is systemic inflammation, which increases the risk of a plethora of autoimmune-, neurodegenerative-, or endotoxic diseases. General inflammation has the goal of reacting to either exogenous, microbial and viral (PAMPs), or endogenous, trauma, necrosis, chemicals, or impaired cellular function (DAMPs), factors (Carlberg et al., 2016). Systemic inflammation can either be acute or chronic, where chronic inflammation can last up to years due to internal mismanagement of the resolution of inflammation (Carlberg et al., 2016). Microglia can detect peripheral infections; this communication is mediated through blood cytokines and neuronal communication from peripheral infections (Konsman et al., 2002; Lacroix et al., 1998). Specifically, the communication to microglia is reliant on the spreading of pro-inflammatory cytokines through circumventricular organs, which lack a proper BBB to filter for these compounds or by using receptors in their endothelium (Lacroix et al., 1998; Ek et al., 2001). Innervation of these microglia by these PAMPs can ultimately result in neuroinflammation (Jiao et al., 2018).

Neuroinflammation induced by peripheral infections has been researched with contradicting results. Historically, LPS and double-stranded RNA studies mostly showed a positive correlation between cytokine abundance in the CNS and Aβ depositions, but some studies found no significant differences in a

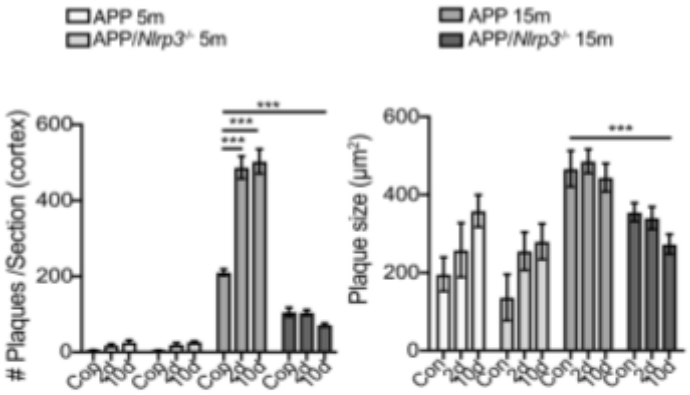

Figure 4: Difference in plaque formation after challenge between NLRP3 expressing and mice.
Bar graphs showing both plaque numbers and size for each group. Each group has three bars; control without LPS challenge, 2d: 2 days after LPS challenge, 10d: 10 days after LPS challenge. Challenges done after 15 months when first plaques were found (*P < 0.05, **P < 0.01, ***P < 0.001). (Graph courtesy of Tejera et al. (2019).

variety of mouse models for AD (APP/PS1, APP23, 3xTG-AD, 5xFAD, among others) (Xie et al., 2022). In a recent study by Tejera et al. (2019), they tested how microglia changed with LPS-induced systemic inflammation, aiming to understand how microglial Aβ clearance was affected by such stimuli. They used Cx3cr1-eGFP−/+ mice to display microglial phenotypical changes during inflammation. The glial cells

shrank in total area and had significantly fewer branches, a bigger soma, and shorter branch length (Tejera et al., 2019). Hypothesized to promote phagocytosis. In the same paper, they followed up by looking at the NLRP3-inflammasome, thought to be a main driver in microglial neuroinflammation (Vanaja et al., 2015). Nlrp3−/− mice were used to assess its effect on microglial phenotype after LPS administration (Tejera et al., 2019). The mice showed significantly more branching, branch length, and maximum branch order ten days after the immune challenge compared to wild types (Tejera et al., 2019). Lastly, they crossbred the Nlrp3−/− mice with APP/PS1 mice, testing plaque deposition between the two groups after an LPS challenge. It was shown that after 15 months, when the plaques started forming in both groups, the APP/PS1/Nlrp3−/− mice showed significantly fewer plaques than their APP/PS1 peers (Figure 5) (Tejera et al., 2019). Further analysis revealed a possible mechanistic reason: plaque clearance relied on distance from the plaque (Tejera et al., 2019). APP/PS1 microglial cells could not sense or reach the plaques due to their lesser branching and total area, caused by the neuroinflammation, as shown in the first experiment (Tejera et al., 2019). In summary, this revealed that a systemic inflammatory response can hinder microglia in the clearance of Aβ by activating the NLRP3-inflammasome, which is in line with previous research by Heneka et al. (2012).

3.4 Therapeutic, diagnostic, and/or preventative targets for AD?

In the now discussed research, it has become apparent that microglia play a crucial role in the development, progression, and stopping of pathogenic amyloid plaques. This creates its allure as a therapeutic or diagnostic target for AD.

Firstly, the recent discoveries on the state change of microglia as a response to DAMPs and PAMPs show the importance of controlling and monitoring DAM-like progression in microglia. The topic is incompletely understood as of now, but the potential for diagnostics through gene expression and immuno-based imaging can be a more accurate way of illuminating not only AD, but a plethora of other neurodegenerative and neuroinflammatory diseases in their early stages.

Secondly, the discovery of genetic predispositions for LOAD allows for insights into the mechanistic features of the pathogenesis of amyloidosis. Proteins that are crucial for the regulation of a homeostatic and non-toxic environment are high-priority targets for mediation. APOE has been eyed as a possible target for the treatment of plaque formation and slowing of cognitive decline. Due to it being the highest risk gene for AD and its importance in the aggregation of plaques, many labs have tried to find ways of influencing its impact within the CNS. In two studies, an immunotherapy was used to alleviate APOE-burden, specifically APOE4 (Kim et al., 2012; Liao et al., 2014). Intraperitoneal injection of HJ6.3, the monoclonal antibody in question, specific against APOE, is effective in reducing amyloid deposition by modulating microglial responses to be less pro-inflammatory (Kim et al., 2012; Liao et al., 2014). It even improved cognitive function while not affecting plasma cholesterol levels (Liao et al., 2014). Another option would be to target the binding of APOE to its receptors. Mimetic peptides can either mimic HDL and bind to APOE to lead to an increase in expression of APOE and fight the plaques through lipidation or block the binding of the protein to reduce immunoreactivity of microglial cells, improving cell survival rates in AD models (Chernick et al., 2018; Krishnamurthy et al., 2020). These preclinical data show the potential of peptides and

immunotherapies in targeting APOE. In the case of targeting specifically APOE4 as a genetic factor, CRISPR/Cas9 could be explored for correcting the risk gene with a healthy APOE3/3 genotype, alleviating the risk of disease. Unfortunately, in vivo testing of the technology has yet to provide boundary-breaking results. The limitations of its current state make it difficult to be successful, with timing, neuroanatomical specificity, and potential off-target effects being points of importance before proper usage can be assumed.

Another protein of interest is TREM2, the recently discovered genetic SNPs that both heighten and lower the risk of AD give theoretical reasoning as to why it could be exploited as a therapeutic target (Long et al., 2024). Based on research conducted on its function, its signal inducers have become increasingly promising, like AL002 (Long et al., 2024). A current phase II clinical trial, INVOKE II, on the activator has reported that AL002 did not significantly slow or resolve the amyloidosis problems on imaging scans and liquid biomarker tests (Alector, 2024). Although pharmacodynamic engagement was seen through increases in the patients' soluble TREM2 (sTREM2), no significant benefits were found (Alector, 2024). Plenty of questions remain as to whether TREM2 can be a target for therapeutics, but it must be noted that there were a lot of limitations to the study. All individuals were in the early stages of AD, which may not be the correct period for elevating TREM2 levels (Ma et al., 2025). Additionally, dosage and treatment time might be insufficient to see results (Ma et al., 2025). Although the trial did not reach its clinical end goals, it provided valuable insights into TREM2 treatment for AD (Ma et al., 2025).

4 Discussion

The fight against amyloidosis is a constant dance between pathogenic protein aggregates and microglia, which try to keep order and react accordingly to the threat of neurodegeneration. Constant exogenous pressure and a multitude of unfortunate defects can have major effects on the risk of disease development. But those same defects gave us insights into mechanisms of action that allow us to develop more precise medications to try to restore balance alongside the resident innate immune cells of our CNS.

Microglia, their function is to keep the brain in homeostatic balance while also reacting to signals induced by PAMPs and DAMPs (Li et al., 2013). They exhibit a large array of different surface receptor families, of which two receptors are key components of the mechanism that allows the phagocytosis of Aβ: Mer and Axl. These RTKs are necessary for the correct clearance of toxic amyloid deposits (Huang et al., 2021). While those receptors allow for phagocytosis, others allow the microglia to change states to ones that allow a better response toward different pathological markers. This transition to a DAM-like state was only recently documented and has since allowed for a new field to flourish, trying to understand how these highly adaptive cells function (Keren-Shaul et al., 2017). These findings abolish the old view on how microglia were either active or passive; by showing the wide range of regulatory states the cells can be found in.

LOAD has been found to have a multitude of different genetic predispositions in high-risk genes, like *APOE, TREM2,* and *CD33,* among many others (Castellano et al., 2011; Basha et al., 2023; Estus et al., 2019). All of which impact the ability of microglia to deal with plaques, both negatively and positively, in the case of rs3865444 in CD33 (Estus et al., 2019).

Systemic inflammation can induce microglia to cause neuroinflammation, which is done through a pathway in which the NLRP3 receptor is necessary (Tejera et al., 2019). Chronic inflammation of microglial cells leads to the shrinking of their branches, inhibiting their ability to detect and properly deal with pathogenic compounds (Tejera et al., 2019).

Furthermore, several trials have explored the possibility of targeting microglial-expressed genes and functions for therapeutic enlightenment. Some promising preclinical studies showed that peptides and immunotherapies for the APOE genes have potential, while the INVOKE II clinical study showed no significant results, raising questions on the viability of TREM2 as an additional target (Kim et al., 2012; Liao et al., 2014; Alector, 2024). However, many limitations of the trials allow for proper evaluation and require deeper investigation into dosage and timing among other variables (Alector 2024; Ma et al., 2025).

This research illustrates the presence of an ever-growing research front on the importance of understanding microglial functionality, to find a solution to the detrimental problem that Alzheimer's has and will become in the future. It compiles the recent findings that shifted the old view on microglia and their dichotomous states to a complex spectrum-like dynamic.

Recommendations regarding future research are mostly centred around a fuller understanding of internal mechanisms. The multifaceted nature of microglia has only recently been brought to light, and many of its more exact states have yet to be documented. Understanding these intermediate states and where the checkpoints for further differentiation lie might allow us to assist in fighting disease in the already vulnerable CNS. Additionally, more research needs to be focused on the proper evaluation of treatment

options, based on previously acquired preclinical data. Risking the lives of patients on incompletely understood compounds is reckless, but promising results have been shown, and more rigorous data and evidence need to be found. Specifically, to eliminate our lack of understanding of confounding factors like dosage and timing, which could have halted the INVOKE II program. But most of all, all research into fighting an incoming epidemic of sickly elderly is beyond helpful in finding how we can alleviate the looming catastrophe for hospitals, families, and the economy if no changes are made.

5 Disclaimer

This thesis has been written with the assistance of AI. The usage was limited to grammar correction and proofreading purposes (Grammarly™, Grammarly Inc.; ChatGPT™, OpenAI). Nonetheless, the entire transcript has been written by the author.

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