**International Journal of Biology and Life Sciences**
ISSN: 2957-9511 | Vol. 12, No. 2, 2025

# Phenotypic Transformation Mechanisms and Therapeutic Targets of Microglia in Alzheimer's Disease

**Huiming Deng ***

School of Medicine, Inner Mongolia Medical University, Hohhot, Inner Mongolia, 010110, China
*** Corresponding author Email:** 15548301129@163.com

**Abstract:** The aim of this paper is to summarize the mechanism of phenotypic transformation of microglia and to explore the impact of pathological changes in Alzheimer's disease (AD) on its phenotypic regulation, with a view to providing new targets for the treatment of the disease. Recent studies have shown that microglia phenotype is highly dynamic, continuous and plastic, breaking through the limitations of the traditional M1/M2 dichotomy and laying the foundation for a deeper understanding of the AD process. By reviewing the literature related to therapeutic targets of recent hotspot studies, this paper proposes that modulation of microglia phenotype can delay the progression of AD, which provides a possible direction for realizing precision targeted therapy.

**Keywords:** Alzheimer's Disease; Microglia; Phenotypic Transformation; Therapeutic Targets.

## 1. Introduction

Alzheimer's disease is the most common type of dementia, accounting for about 70 percent of all cases. [1] As the population ages, there were 48.3 million people living with Alzheimer's disease globally in 2016, and it is projected that by 2050, 152 million people will be affected. And Alzheimer's disease-related mortality is increasing significantly worldwide.[2] Alzheimer's disease (AD) is an irreversible neurodegenerative disease, the main pathological changes are Aβ plaque deposition, tau protein degeneration, neuroinflammation and so on. It is more common in people over 65 years old, and is more common in women than in men. The cause of AD is still unclear, and it is thought to be due to a combination of factors that lead to the development of AD. The cause of AD is still unclear, and it is thought to be due to a combination of factors that lead to the development of AD. Early clinical manifestations include memory loss, cognitive decline, and behavioral changes. When the disease progresses to advanced stages, patients gradually lose their ability to perform their daily lives and eventually become completely dependent on others for care. When the disease progresses to advanced stages, patients gradually lose their ability to perform their daily lives and eventually become completely dependent on others for care. This has a great impact on the health and life expectancy of the elderly.[3]

AD is a long latency, progressive disease, and some biomarkers can be detected as early as 20 years before onset.[4] However, there are no specific drugs available, which can only slow down the progression of the disease. Therefore, we should utilize this therapeutic window to make early detection and diagnosis, and intervene as early as possible. Therefore, we should utilize this therapeutic window to make early detection and diagnosis, and intervene as early as possible to stop the disease progression or even reverse it. Previous therapeutic strategies have focused on treating AD by inhibiting the overdose of AD. Previous therapeutic strategies have focused on treating AD by inhibiting the over-activation of microglia or enhancing their phagocytosis; however, microglia play different roles in different stages of AD, and simply inhibiting the over-activation of microglia is not the only way to prevent AD. stages of AD, and simply inhibiting the activated state and maintaining the resting state can lead to uncontrolled neuroinflammation, decreased Aβ clearance, and increased neurotoxicity. clearance, and increased neurotoxicity.[5] In recent years, with the increasing research on microglia, scholars have begun to focus on their complex phenotypes and functions, with a view to precisely regulating the functional state of microglia and transforming microglia from destroyers to protectors for the treatment of a variety of microglia. protectors for the treatment of a variety of central nervous system diseases, including AD. [6-10]

## 2. Overview of Microglia

### 2.1. Microglia Physiology

Microglial (MG) cells are resident immune cells in the CNS. Unlike other CNS cells, MGs do not originate from the neural ectoderm but from yolk sac fetal macrophages, which settle in the CNS and possess the ability to self-renew. Under physiological conditions, MGs mainly play immune defense, phagocytosis, synaptic pruning, synaptic remodeling, maintenance of the blood-brain barrier, neurotrophic and protective roles.

MGs make up about 5-6% of all cells in the CNS, and they are relatively evenly distributed throughout brain regions; however, MGs are not a single, undifferentiated population of cells, and they do not have similar morphologic, functional, and biologic properties throughout the CNS, and this heterogeneity is influenced by region of distribution, age, and gender.[11] Researchers integrated 19 single-nucleus RNA sequencing (snRNA-seq) and single-cell RNA sequencing (scRNA-seq) datasets from a wide range of neurodegenerative diseases, containing a total of 241 samples, to construct a human microglia atlas and classify Alzheimer's disease-associated MGs into groups based on differences in gene expression patterns, functional characteristics, disease states and pathological features, tissue and cellular origin. Alzheimer's disease-associated MGs were classified into 9 subpopulations.[12] By understanding the dynamics of different subpopulations in disease progression, a deeper

understanding of the pathomechanisms of AD can be achieved, which can help develop interventions targeting the early stages of the disease.

The phenotype of MG is determined by the microenvironment, and changes in the microenvironment can lead to changes in the phenotype of MG, both during normal development and in disease states. The emergence of the DAM (disease-associated microglia) state has been found to be induced by the microenvironment surrounding Aβ plaques, and the DAM phenotype has been found to be prevalent in a wide range of diseases. Structural, molecular, and cellular changes occur in the brain with age, which, similar to the process of disease development, result in microenvironmental changes that cause phenotypic transformations in microglia, so that aging can cause significant morphological changes in MG. Of course, the heterogeneity of MG phenotypes is not only reflected in differences in morphology and function, but also in changes at the level of gene transcription. Happily, the state of MG is plastic, and the results demonstrate that MG can be restored to full homeostasis after removal of the causative factors, and reversing MG from the DAM state to the homeostatic state is a future strategy for the treatment of a variety of neurological diseases.[13]

In Alzheimer's disease, MG, through membrane surface receptors, senses changes in the microenvironment and is then activated to the M1 type, which functions in phagocytosis of abnormal protein deposits and releases inflammatory factors to initiate an inflammatory response. However, MG is not only activated and resting state, according to the research, there is a highly dynamic phenotype of MG, with different morphology, exerting different functions.

## 2.2. Microglia and Alzheimer's Disease

The pathogenesis of AD is still unclear, and there are many hypotheses related to its pathogenesis, two of which are widely accepted: the amyloid-β (Aβ) cascade and hyperphosphorylation of tau proteins. the Aβ cascade hypothesis suggests that Aβ is deposited in the form of neuroinflammatory plaques, which can induce AD by damaging neuronal cells. excessive production of amyloid and impaired clearance of amyloid may lead to amyloid accumulation in the brain, promoting the development of AD and initiating a harmful cascade reaction involving tau pathology and neurodegeneration. accumulation of amyloid in the brain, promoting the development of AD and initiating a deleterious cascade of responses involving tau pathology and neurodegeneration.[14] In turn, tau proteins can affect axonal transport and growth, neuronal polarization, and thus normal neuronal and brain function.[15]

MG plays an extremely complex role in the pathological process of AD, and MG can both prevent and exacerbate CNS disease.Aβ induces MG phagocytosis, release of inflammatory factors, and proliferation.Aβ promotes the secretion of proinflammatory cytokines and neurotoxic substances by MG: these include tumor necrosis factor-alpha (TNF-α), IL-1, IL-6, IFN-γ, and reactive oxygen species.[16] MG can uptake tau proteins, tau proteins may in turn lead to MG activation, and activated MG may be directly or indirectly involved in the process by which tau proteins are repackaged into exosomes, thus facilitating the spread of tau pathology. In the early stages of the disease, MG is activated to play a preventive role by removing Aβ, inhibiting the hyperphosphorylation of tau proteins, and producing neurotrophic factors, thus slowing down the progression of AD; this type is known as M2 (anti-inflammatory type). However, when the disease worsens, persistent inflammation, and overexposure to oxidative environments lead to persistent activation of MG, which results in neuroinflammation, oxidative stress, and neurotoxicity; this type is known as M1 (pro-inflammatory).

When activated, MGs produce different phenotypes, and since the 2010s, microglia have been simply categorized as "M1" (pro-inflammatory) and "M2" (anti-inflammatory) based on concepts established in macrophages. However, in recent years, thanks to the development of scRNA-seq and snRNAseq technologies, researchers have discovered more new phenotypes of microglia and have used tools such as white matter genomics, metabolomics, transcriptomics, morphology, and epigenetics to study the more complex morphologic functions of microglia.[17]

## 2.3. Microglia Phenotype

The phenotypes of MG, in addition to the traditional M1/M2 dichotomy, include the following new phenotypes.

Dark microglia (DM) are a phenotype that is significantly increased in the brains of AD patients, named for the electron-dense "dark" appearance of their nucleoplasm and cytoplasm.DM is a pro-neurodegenerative phenotype, with dilated endoplasmic reticulum, swollen or vacuolated mitochondria, increased lipid droplets, and disturbed lipid metabolism. It is characterized by high expression of inflammatory factors and ISR markers and reduced phagocytosis, and ISR activation results in secretion of toxic lipids, which lead to the spread of tau proteins through secretion of exosomes.[18]

DAM (Disease-Associated Microglia), is a novel phenotype first identified by single-cell RNA sequencing (scRNA-seq) by Ido Amit's team and Michal Schwartz's team in the 5xFAD Alzheimer's disease mouse model.[19] This is a transition state that is both protective and destructive. DAM is transcriptionally characterized by upregulation of APOE, TREM2, and downregulation of P2RY12, TMEM119.Beta-amyloid is cleared by upregulation of the TREM2-APOE pathway, but may lead to lipid accumulation due to lysosomal dysfunction. In addition, DAM shifts from oxidative phosphorylation to glycolysis for biosynthesis via metabolic reprogramming, but may lead to mitochondrial dysfunction and iron metabolism disorders. In AD, DAM accumulates around Aβ plaques and may exacerbate neurotoxicity. Thus, DAM plays a protective role in early AD but may translate into a deleterious phenotype in later stages.[20] In addition, some studies have confirmed that DAM is also present in Parkinson's disease, ALS, and aging brain, suggesting that it may serve as a common target for intervention in neurodegenerative diseases.[21]

LDAM (Lipid-droplet-accumulating microglia), or lipid droplet-accumulating microglia, is a subpopulation of microglia newly identified in aging and multiple neurodegenerative diseases, characterized by lipid droplet accumulation, defective phagocytosis, and a high degree of inflammation.The protrusions of LDAM are shortened, with a reduction in branching, and massive aggregation of intracytoplasmic lipid droplets. Genes related to innate immunity or lipid metabolism are upregulated, and homeostatic genes Tmem119 and P2ry12 are downregulated. In the 5XFAD model, LDAM was highly aggregated around Aβ plaques and highly overlapped with regions of localized synaptic loss. Drivers such as Aβ proteins, aging and genetics

convert MG to the LDAM phenotype.[22] In particular, harboring the APOE4 gene predisposes MG to abnormal lipid metabolism, which in turn converts it to the LDAM state.

The dendrites of senescent microglia are reduced, and although senescent microglia are often found around Aβ plaques in the brains of AD patients, defective phagocytosis leads to clearance failure. Large numbers of lipofuscin granules and lipid droplets appeared in their cytoplasm, suggesting disturbed lipid metabolism. Targeting the cholesterol pathway to remove senescent microglia may become a new strategy for AD treatment. [23]

# 3. Research on Phenotypic Transformation Mechanisms and Therapeutic Targets:

## 3.1. Pathologic Changes in AD

One of the earliest pathological changes in AD is the abnormal processing and deposition of Aβ proteins. Early on, Aβ proteins are predominantly found in diffuse plaques, with dense and fibrotic plaques not yet present or in very small quantities, and these abnormal deposits preferentially accumulate in specific areas of the cerebral cortex, with the hippocampus being the earliest area to be affected. [24]Aβ plaques cause neuronal damage, and the researchers found that synapses around Aβ plaques are significantly reduced, especially excitatory synapses, and that this synaptic loss is largely confined to the vicinity of the plaques in the early stages of the disease, spreading progressively to a wider range of brain regions as the disease progresses[25]. The proportion of fibrotic plaques in the mid- to late-stage of the disease progressively increases, causing further neuronal damage.

Early Aβ plaques, although relatively low in neurotoxicity, have induced changes in the local microenvironment, leading to phenotypic transformation of MG. When Aβ diffuse plaques begin to be deposited, MGs shift from a resting to an activated state and rapidly migrate toward the site of Aβ aggregation, recognizing Aβ through receptors such as TREM2, CD36, and TLR4, phagocytosing and degrading Aβ in the diffuse state. If TREM2 is mutated, it impairs the ability of MGs to scavenge Aβ, which correlates significantly with the risk of AD.MGs release proinflammatory cytokines after activation, and the early inflammatory response is usually moderate, which facilitates the recruitment of more MGs to synergistically clear Aβ. prolonged activation of MGs, however, leads to chronic inflammation. Interventions at this stage focus on enhancing TREM2 function , inhibiting excessive inflammation, and aim to maintain the protective function of MG.

## 3.2. Aβ Acts on Piezo Proteins to Regulate Microglia

In addition to their ability to respond to biochemical signals from the surrounding microenvironment, MGs can also sense mechanical signals in the microenvironment. Piezo proteins, the first family of mechanosensitive cation channels identified in mammals, convert mechanical force stimuli into electrochemical signals and play key roles in tactile and nociceptive sensation, vascular development, immune response, and neurodegenerative diseases.[26] Piezo1 in the MGs protein senses the stiffness of Aβ plaques in the brain of AD patients. In the early stage of preclinical AD, soluble Aβ plaques, in the form of monomers or oligomers, inhibit calcium ion inward flow by directly binding to Piezo1 channels and inhibit Piezo1 channel activity, resulting in the inability of MG to remove soluble Aβ in a timely manner. As the disease progresses, fibrotic Aβ activates Piezo1 channels, triggering calcium ion inward flow, causing MG to migrate toward the plaques and phagocytose the fibrotic Aβ, which has a protective effect on the nervous system. In the late stage of the disease, fibrotic Aβ cross-links and forms rigid plaques, whose stiffness increases significantly, resulting in sustained activation of Piezo1, leading to a burst of ROS (reactive oxygen species), at which time the MG is transformed into a pro-inflammatory phenotype. RNA sequencing analysis showed that Piezo1 activation upregulated the expression of cytoskeletal dynamin (e.g., Rho GTPases, integrins), phagocytosis-related genes (e.g., TREM2) and promoted the transformation of MG to a pro-inflammatory phenotype. conversion of MG to an anti-inflammatory phenotype. Knockdown of Piezo1 resulted in down-regulation of these pathways, loosening of plaque parcels and increased spreading[27]. In contrast, Yoda1, a Piezo1-specific agonist, significantly facilitated MG migratory capacity and phagocytosis of Aβ42 by activating Piezo1 channels. In AD model mice (5xFAD), injection of Yoda1 for 12 consecutive days increased MG aggregation toward amyloid plaques and reduced plaque formation[28]. It was found that there was cross-regulation of inflammatory responses and mechanistic signaling, and that calcium inward currents triggered by Piezo1 activation activated NF-κB/NLRP3, released TNF-α/IL-1β, and caused cytoskeletal remodeling. Piezo1 sensitivity is enhanced, which leads to a vicious cycle. Resveratrol has antioxidant, anti-inflammatory and neuroprotective effects, and by scavenging ROS, it can inhibit pro-inflammatory signaling pathways such as NF-κB, thus reducing the release of inflammatory factors such as TNF-α and IL-6, and indirectly attenuating oxidative damage and inflammatory responses triggered by the Piezo1 pathway[29]. In summary, the earlier Aβ plaques activate Piezo1 to initiate inflammatory responses and enhance phagocytosis. At this time, the inflammatory response and mechanistic signaling are mutually reinforcing and balanced, providing a protective effect. However, in the late stage of the disease, the stiffness of rigid Aβ exceeds the critical point, leading to the continuous activation of Piezo1, massive release of inflammatory factors, further upregulation of the expression and sensitivity of Piezo1, and the formation of a vicious cycle. Therefore, the therapeutic window for enhancing Piezo1 activity should be early to mid-stage, and anti-inflammatory should be the main focus in the late stage.

## 3.3. Regulation of Microglia Phenotypic Transformation by TREM2

TREM2 (Triggering Receptor Expressed on Myeloid cells 2) is an immunomodulatory cell surface receptor expressed primarily in microglia of the brain.TREM2 has a dual role in the pathologic progression of AD, protecting neurons by modulating MG function in the early stages and possibly exacerbating the pathologic process by dysfunction in the later stages. may exacerbate the pathological process due to dysfunction. Different therapeutic strategies are needed to characterize TREM2 function at different stages.

In pre-Alzheimer's disease (AD), TREM2 is synergistically up-regulated with APOE to promote the conversion of microglia from homeostasis to disease-associated microglia (DAM), enhance phagocytosis of Aβ plaques, and protect

neurons from damage. Through metabolic reprogramming, MGs are induced to shift from glycolysis to oxidative phosphorylation, enhancing energy efficiency and limiting plaque formation and peripheral neuronal damage. In late AD, persistent Aβ plaque accumulation and neuroinflammation lead to changes in the microenvironment. overactivation of MG may trigger a neurotoxic response, releasing proinflammatory factors and reactive oxygen species, leading to neuronal injury. In brain regions with limited clearance (e.g., iAD-lim), TREM2 drives the expression of inflammatory genes (e.g., A2M, LAMP1) through the TYROBP adapter (Fig 2h), which translates into a neurotoxic phenotype and exacerbates neurological damage. In addition, TREM2 function may be impaired by mutation or chronic inflammation, rendering it unable to efficiently modulate MG responses and thus exacerbating neurodegenerative pathologies. [30]

TREM2 agonists activate downstream signaling pathways by binding to the extracellular structural domain of TREM2 and mimicking its natural ligands, such as Aβ, lipids, and ApoE, thereby enhancing the phagocytosis of Aβ by MGs, reducing the aberrant phosphorylation and seeding of tau proteins, promoting glucose metabolism, and maintaining homeostasis. Currently developed TREM2 agonists mainly include AL002, 4D9, and HZ-AD16. AL002 has entered clinical phase II and may become a key component of AD immunomodulatory therapy in the future. [31]

### 3.4. Regulation of Microglia Phenotypic Transformation by APOE

Apolipoprotein E (APOE) is a major genetic risk factor for AD, with the APOE4 allele significantly elevating the risk of AD. The APOE4 allele has a significant effect on the functional state of MG, promoting the conversion of MG to a pro-inflammatory phenotype. APOE, as a key protein, plays a crucial role in the human body, and participates in a variety of physiological processes, such as lipid metabolism, neural repair and immunomodulation, among other physiological processes.

In AD patients and transgenic mouse models, APOE4 expression is associated with higher Aβ load, more severe tau pathology, and earlier cognitive decline. Several studies have shown that reducing or depleting ApoE attenuates neuroinflammation and alleviates pathological changes in various mouse models of amyloid and tau pathology. Reducing ApoE4 prior to plaque deposition significantly reduced Aβ pathological changes, and reducing ApoE4 after Aβ seeding reduced plaque-associated nerve sheath dystrophy. [32]

Apolipoprotein E4 (APOE4) causes chronic activation of MG by interfering with the triglyceride (TG) metabolism pathway[33]. The energy metabolism pattern of MG is altered, as evidenced by a reduction in mitochondrial oxidative phosphorylation and an enhancement of glycolytic pathways. Upon neuronal conditioned medium (CM) stimulation, APOE4 microglia exhibited activation of pro-inflammatory transcription factors such as NF-κB, STAT4, as well as decreased expression levels of anti-inflammatory factors (e.g., CBL, PRDM1). Downregulation of the expression of the homeostatic marker P2RY12 in conjunction with upregulation of the pro-inflammatory marker ADORA2A suggests a shift to a pro-inflammatory phenotype in MG. [34] significantly ameliorated the APOE4-associated inflammatory phenotype by inhibiting diacylglycerol acyltransferase (DGAT), a key enzyme in triglyceride synthesis, providing a new target for AD treatment. The study used a model of human pluripotent stem cell (iPSC) differentiation into MG, combined with CRISPR gene editing and pharmacological interventions to validate the necessity of lipid droplet accumulation for microglia activation. [35]

DGAT inhibitors are a class of compounds used to inhibit Diacylglycerol Acyltransferase (DGAT). It was found that DGAT inhibitors significantly down-regulated the expression of several inflammation-related genes, such as IL-6, IL-1β, and TNF-α, upon treatment of APOE4 microglia. The expression of disease-related genes was suppressed, while the expression of homeostatic genes was upregulated (Figure 6E and Table S6). This suggests that APOE4-associated pathology can be reversed by regulating triglyceride metabolism. [35]

### 3.5. Regulation of MG Phenotypes by the TREM2-APOE Pathway

APOE and TREM2 (myeloid triggering receptor 2) synergistically regulate the immunometabolic function of MG in AD, and together they affect neuroinflammation, pathological protein clearance and neuronal damage. They constitute the "APOE-TREM2 axis", which is the core regulatory network of AD pathology. APOE is a ligand for TREM2, and the combination of the two activates phagocytosis and inflammatory responses of MG. APOE4 may lead to MG overactivation through aberrant activation of TREM2 signaling, which may in turn exacerbate neuroinflammation and synaptic damage.

TREM2 and APOE expression was significantly increased in immunized MG and positively correlated with antibody titer. Promotes MG recruitment to Aβ plaques, forming a DAM phenotype and enhancing Aβ phagocytosis. Undergoes metabolic reprogramming, exhibiting enhanced oxidative phosphorylation and reduced glycolysis, suggesting that optimization of energy metabolism supports scavenging function. In addition, a reduction in stress genes such as HSPs (heat shock proteins) and up-regulation of repair genes such as SPP1 (bone bridging proteins) and FGFR3 (fibroblast growth factor receptor 3) to promote tissue repair and neuron-microglia communication were also demonstrated. [36]

## 4. Conclusion

Microglia (MG) are not only resident immune cells in the nervous system, but also play a key role in the pathological process of Alzheimer's disease (AD). During the development of AD, MGs exhibit both protective and pathogenic properties. The phenotype of MGs is spatiotemporally specific, highly dynamic, phenotypically plastic and continuous. At various stages of the disease, MG can be transformed into different phenotypes due to the different pathological environments in which they are found. The same therapeutic target may produce diametrically opposite effects at different stages of the disease. For example, in the early stage of AD, MG exerts mainly anti-inflammatory effects under the regulation of Piezo1 protein; however, in the late stage of AD, this regulatory capacity is dysregulated, resulting in the transformation of MG into a pro-inflammatory phenotype. TREM2 protein exhibits protective effects in the early stage of AD, while it may exert damaging effects on the disease in the late stage. In contrast, APOE proteins exhibit deleterious effects regardless of the stage of AD. Therefore, differentiated

therapeutic strategies should be adopted for different pathological stages of AD. However, the key issue is how to accurately determine the pathological stage of the patient and the phenotype of MG at this time. Given that AD is characterized by high heterogeneity, dynamic evolution, and significant inter-individual variability, future research should be devoted to the development of individualized therapeutic strategies, to achieve the precise spatiotemporal and spatial-specific regulation of microglia function, and to actively promote the therapeutic model of synergistic multi-target intervention.

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