Alzheimer's Disease Neuropathology and Epidemiology

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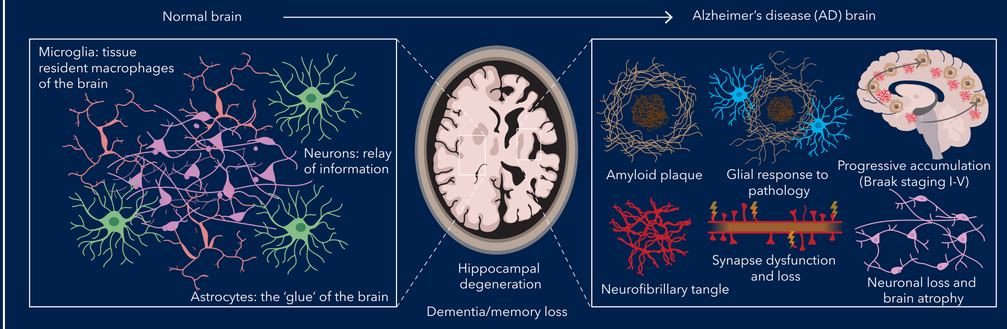
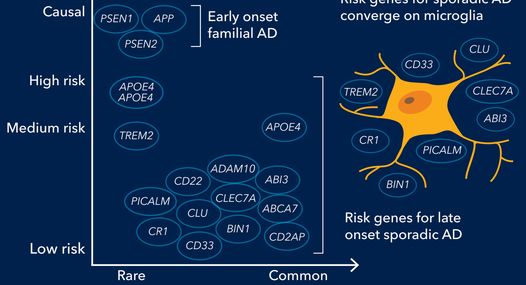
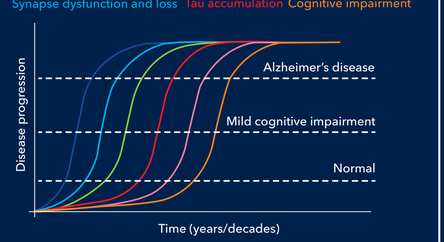
The leading cause of dementia worldwide is Alzheimer's disease (AD), which is a debilitating and progressive neurodegenerative disease. The main risk factor for AD is age, whereby more than 30% of individuals aged over 85 years have AD. Given the increasing aging population, it is projected that AD cases will rise dramatically each year. AD patients present with continuing memory loss, and are histopathologically characterized by progressive and region-specific deposition of amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the brain. These hallmarks are accompanied by neuronal loss and brain atrophy particularly of the hippocampus, a region which is associated with memory. The molecular changes are thought to begin decades before patients experience memory loss; at diagnosis they may already have lost 40% of their hippocampus. Currently there is no cure for AD so there is an urgent need for research into molecular and cellular mechanisms in order to identify therapeutic targets to slow down or prevent disease.

Shift in the field: a genetics perspective

5% of AD cases are attributed to early onset autosomal dominant AD, which is caused by mutations in PSEN1, PSEN2, or APP. APP encodes for Aβ protein, which makes up plaques; PSEN1 and PSEN2 encode for enzymes involved in the proteolytic cleavage of Aβ. 95% of cases are sporadic late onset AD (LOAD) without a causative genetic mutation, suggesting that other factors contribute to disease onset. Age and comorbidity, alongside some environmental factors have been suggested to increase risk. In recent years, several human genome wide association studies (GWAS) have identified multiple mutations that significantly increase the risk of developing LOAD. Most of these genes are not expressed by neurons but are predominantly immune genes involved in phagocytosis and lipid metabolism including *APOE, TREM2, CD33, CLEC7A, CD22, CLU* and *CR1*. Many of these genes are either exclusively or highly expressed by microglia, which are the primary tissue-resident macrophages of the brain parenchyma. Since Alois Alzheimer first reported the disease more than a century ago, microglia have been shown to associate with plaques, however, their role was thought to be secondary in disease pathogenesis. The strong influence of genetics and the immune system on disease risk have driven recent research towards the use of a variety of disease models and AD patient tissue; this has highlighted neuro-inflammation and microglia as central players in AD risk and progression.



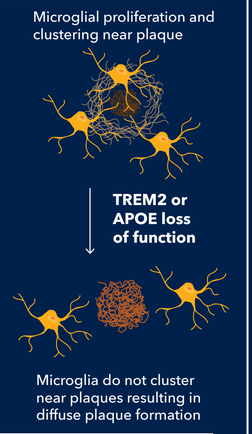




Microglial TREM2: the master regulator?

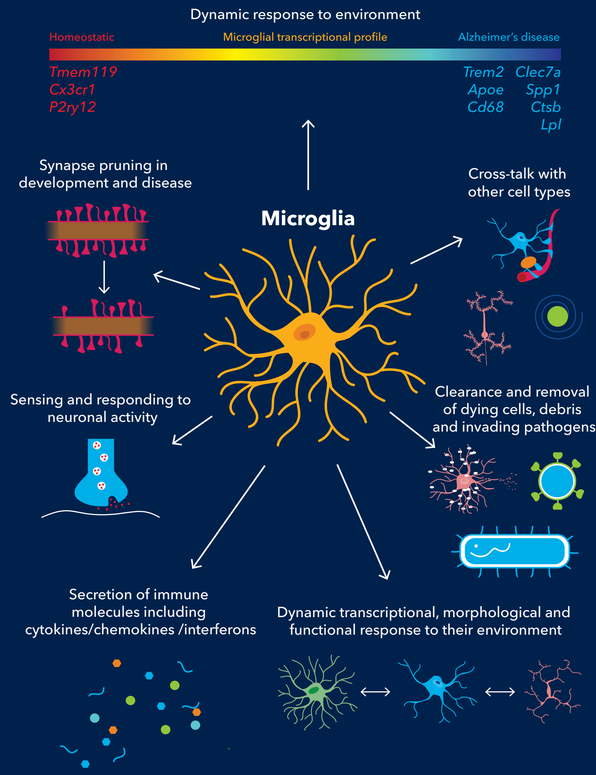
Triggering receptor expressed on myeloid cells 2 (TREM2) is a receptor that belongs to the immunoglobulin superfamily and is expressed on myeloid cells such as microglia in the brain. TREM2 is a key lipid sensor that binds to phospholipids, Aβ, and lipoproteins such as ApoE. TREM2 also exists as a soluble form (sTREM2) which is increased in the CSF of AD patients and can arise from receptor shedding or alternative splicing. Risk mutations in TREM2 have been identified; the greatest risk is attributed to the R47H mutation, which increases risk of developing LOAD by 2-4 times. The loss-of-function mutation prevents normal folding of the protein. Interestingly, gain of function mutations in PLCγ2, downstream in the TREM2 signaling cascade, decrease the risk of developing AD.

Mouse models harboring mutations in TREM2 have been generated to study the role of TREM2 in AD pathogenesis; *in vivo* mouse models of Aβ deposition highlight multiple critical roles for TREM2 in microglial response to pathology. TREM2 has been shown to alter the clustering and proliferation of microglia around Aβ plaques, which in turn affects plaque compaction and diffusion. TREM2 has also been suggested to modulate Aβ- and tau-induced neuritic dystrophy, and to modulate microglial engulfment of synapses in development and in AD models. Finally, TREM2 has been shown to be critical for microglia to transition to disease-associated microglial cell states. These critical functions of TREM2 affect microglial responses to AD pathology and are an active area of research.



Microglia: more than bystanders

Microglia are professional phagocytes of the central nervous system. They are dynamic cells that constantly survey their local milieu for signals of danger, injury, pathogens, and apoptotic neurons, which they clear to retain tissue homeostasis. In addition to their immune functions, microglia monitor changes in neuronal activity and have been shown to be critical for circuit wiring in brain development by pruning excess synapses. In AD, microglia have previously been suggested to release inflammatory cytokines, contribute to the phagocytic clearance of Aβ, and cluster around Aβ plaques alongside reactive astrocytes. Data from multiple groups suggest that microglia are heterogeneous cells that are altered by both age and disease. In particular, multiple disease-associated microglial states have been identified using single-cell sequencing studies in both human and mouse tissue, which are enriched with genes associated with AD risk such as *TREM2* and *APOE*. Work is underway to understand the functional implications this has for disease progression and if these cell states can be modulated.



APOE: the strongest risk

Apolipoprotein E (APOE) is critical for transport of lipids, including cholesterol, to neurons and glial calls. The ε4 allele is the strongest genetic risk factor for LOAD, increasing risk by 3-12 fold in a dose-dependent manner, whereas the ε2 allele is associated with decreased risk of developing AD. In the brain, *APOE* is expressed by multiple cell types including astrocytes, oligodendrocytes and disease-associated microglia, thus has been studied in the context of multiple cellular players. APOE has been suggested to bind to Aβ and play a role in plaque compaction. Studies in both human AD tissue and in mouse models of Aβ pathology have found higher Aβ plaque load in APOE ε4 carriers.

Microglia complementing synapses in AD

One important immune pathway is the complement cascade - an enzymatic cascade of 30 proteins with multiple downstream functions, including inflammation and pathogen elimination. In AD, complement proteins that decorate plaques were thought to be secondary to disease pathogenesis. Mutations in 3 complement genes, *CLU, CR1* and *C1S*, have been identified to significantly increase risk of developing LOAD. This emerging genetic data accompanied by multiple functional studies provides compelling evidence that the complement pathway may be more than a bystander in AD. Complement proteins, including C1q and C3, have been shown to deposit on synapses and mediate microglia-synapse pruning in development. Recent data suggests that Aβ and tau accumulation on synapses upregulates microglial C1q activation leading to complement-dependent microglial synapse-engulfment. This region-specific synapse loss, a key pathological feature of AD, correlates with cognitive decline. Synapse loss is thought to occur prior to overt neuronal loss; a better understanding of the molecular mechanisms that drive early synapse loss in AD may provide a critical window for therapeutic intervention.

Microglia engulf synapses in AD contributing to synapse loss via the classical complement cascade (C1q/C3-CR3)

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Thioflavin T
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Flutax 2

Lysosomes
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Pepstatin A Janelia Fluor® 526

Mitochondria
MitoBrilliant™ 646
Mito-HE
MitoPY1
MitoMark Red I

Cell Indicators and Sensors
DAF FM diacetate
Di 4 ANEPPS

JNK
CEP 1347

PERK
AMG PERK 44
GSK 2606414

APOE
COG 133

Adenosine Receptors
Caffeine
2'-MeCCPA
CGS 21680

σ_1 Receptors
WQ 1
Pridopidine
PRE-084

Phosphodiesterases
PF 04449613

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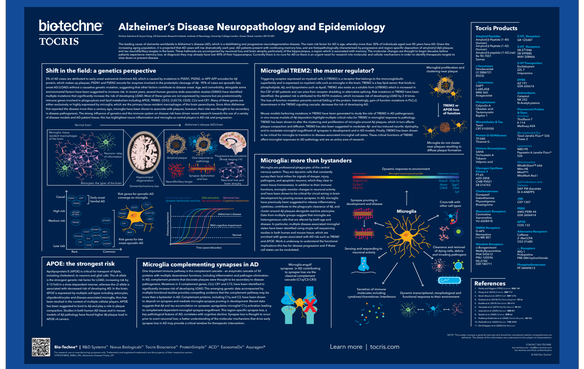
NOTE: This poster conveys a general overview and should be considered neither comprehensive nor definitive. The details of this information are understood to be subject to interpretation.

Wall Poster



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