Alzheimer’s Disease’s Neurodegeneration and Epidemiology

The leading cause of dementia worldwide is Alzheimer’s disease (AD), which is a debilitating and progressive neurodegenerative disease. The majority of AD cases are attributed to early onset autosomal dominant AD, which is caused by mutations in PSEN1, PSEN2, or APP genes. APP encodes for Aβ, a component of the senile plaques in the brain, which is the primary pathological feature of AD, correlates with cognitive decline. Synapse loss is thought to occur decades before patients experience memory loss, at diagnosis they may already have lost 40% of their hippocampus. There is currently no cure for AD and there is an urgent need for research into molecular and cellular mechanisms in order to identify therapeutic targets to slow down or prevent disease.

Microglial complementing synapses in AD

One important immune pathway is the complement cascade - an enzymatic cascade of 30 key proteins. The complement cascade is a key player in the immune system, playing a role in the clearance of pathogens, and apoptotic neurons, which they clear to maintain tissue homeostasis. In addition to their immune function, microglia monitor changes in neuronal activity and have been shown to be critical for memory formation and development by pruning excess synapses. In AD, microglia have previously been suggested to release inflammatory cytokines, contribute to synaptic loss [1.2] and cluster around Aβ plaques alongside reactive astrocytes. Data from multiple studies suggest that microglial activation is heterogeneous, which 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 tissues. This highlights the need for disease progression and these cell states can be modulated.

Microglial TREM2: the master regulator?

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 aggregates such as Aβ. TREM2 also acts as a scaffold that recruits microglia to sites of injury which increases risk of developing AD by 2.6 times. The loss-of-function mutation prevents normal folding of the protein. Interestingly, gain-of-function mutations in PLCy2, downstream in the Trem2 signaling cascade, decreases 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 AD 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 composition and morphology. TREM2 has also been suggested to modulate Aβ and tau-mediated neurodegeneration, and to modulate microglial engulfment of synapses in development and in AD models. Finally, TREM2 has been shown to be critical for microglia to translate 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 tissue for signs of stress or injury, pathogens, and neuropeptides, which they clear to maintain tissue homeostasis. In addition to their immune function, microglia monitor changes in neuronal activity and have been shown to be critical for memory formation and development by pruning excess synapses. In AD, microglia have previously been suggested to release inflammatory cytokines, contribute to synaptic loss, and cluster around Aβ plaques alongside reactive astrocytes. Data from multiple studies suggest that microglial activation is heterogeneous, which 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 tissues. This highlights the need for disease progression and these cell states can be modulated.

TREM2 and APOE loss of function

TREM2 and APOE are key players in the immune system and have been shown to be critical for memory formation and development by pruning excess synapses. In AD, microglia have previously been suggested to release inflammatory cytokines, contribute to synaptic loss, and cluster around Aβ plaques alongside reactive astrocytes. Data from multiple studies suggest that microglial activation is heterogeneous, which 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 tissues. This highlights the need for disease progression and these cell states can be modulated.

References

Microglia have been shown to associate with plaques, however, their role was thought to be secondary. Since Alois Alzheimer first reported the disease more than a century ago, microglia have been suggested to increase risk. In recent years, several human genome wide association studies (GWAS) have identified APOE: the strongest risk factor for Alzheimer’s disease (AD). Many of these genes are involved in phagocytosis and lipid metabolism including PICALM, CR1, BIN1, CD22, ABI3, APOE4, TREM2, and PSEN1. The loss-of-function mutation prevents normal folding of the protein. Interestingly, gain of function mutations in PLCβ superfamily and is expressed on myeloid cells such as microglia in the brain. TREM2 is a key lipid sensor that binds 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 to complement-dependent microglial engulfment. Microglia: more than bystanders, cell states can be modulated. TREM2 has also been suggested to modulate Aβ deposition highlight multiple critical roles for TREM2 in microglial response to pathology.

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