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Review

Microglial Malfunction: The Third Rail in the Development of Alzheimer's Disease

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Studies of Alzheimer's disease (AD) have predominantly focused on two major pathologies: amyloid-β (Aβ) and hyperphosphorylated tau. These misfolded proteins can accumulate asymptomatically in distinct regions over decades. However, significant Aβ accumulation can be seen in individuals who do not develop dementia, and tau pathology limited to the transentorhinal cortex, which can appear early in adulthood, is usually clinically silent. Thus, an interaction between these pathologies appears to be necessary to initiate and propel disease forward to widespread circuits. Recent multidisciplinary findings strongly suggest that the third factor required for disease progression is an aberrant microglial immune response. This response may initially be beneficial; however, a maladaptive microglial response eventually develops, fueling a feed-forward spread of tau and Aβ pathology.

The Pathogenesis of AD

AD is the most common neurodegenerative disease, doubling every 5 years after the age of 65 and affecting one-third of those above the age of 85. Its prevalence is expected to triple by 2050 as a result of an expanding aging demographic [1]. Recent studies indicate that the preclinical development of AD begins years to decades before onset of memory deficits [2]. Over this timeframe, the two pathological hallmarks of Aβ accumulation and tau (microtubule associated protein tau/MAPT) phosphorylation proceed asymptomatically, and are well underway by the time of initial diagnosis. Once predictive biomarkers for AD risk are identified, this preclinical phase will become a critical time-window in which to intervene preventively to delay progression to AD. Later interventions at the stage of dementia are less likely to be disease-modifying because there is already extensive loss of neurons and circuitry at this point.

The 'amyloid cascade hypothesis' of AD causation posits that accumulating $A\beta_{42}$ peptides in the brain lead to hyperphosphorylation of tau and neurofibrillary tangles (NFTs), neuronal loss, and cognitive decline [3]. Since this initial hypothesis, neuropathological studies examining the temporal dynamics and anatomic distribution of amyloid and tau pathologies have expanded our understanding of the pathogenesis of AD (Figure 1). Interestingly, onset of tau pathology can precede Aβ plaque accumulation by decades, and begins to appear in the transentorhinal cortex (TEC) as early as age 20 [2]. By age 50, this Braak stage I–II pathology, also called the 'transentorhinal' stage [4], is found in 50% of subjects [2] but remains clinically silent. Cognitive decline occurs with spread of tau pathology to allocortical regions, also known as the 'limbic'

Trends

The preclinical course of AD spans years to decades before the onset of cognitive decline. Early appearance of $A\beta_{42}$ and tau pathologies are initially clinically silent and do not overlap anatomically. With progression to AD, these pathologies converge and spread from hippocampus to connected circuits.

Microglia play crucial roles in maintaining homeostasis in brain by clearing misfolded proteins and controlling inflammation.

GWAS and systems-biology approaches have identified the microglial immune response as a dominant factor in AD risk.

Studies in AD model mice demonstrate that healthy microglial functions are lost with progression of amyloid pathology.

A maladaptive microglial immune response may be the precipitating factor underlying the escalation of pathology to AD.

Reprogramming microglia to more healthy states is a potential therapeutic direction.

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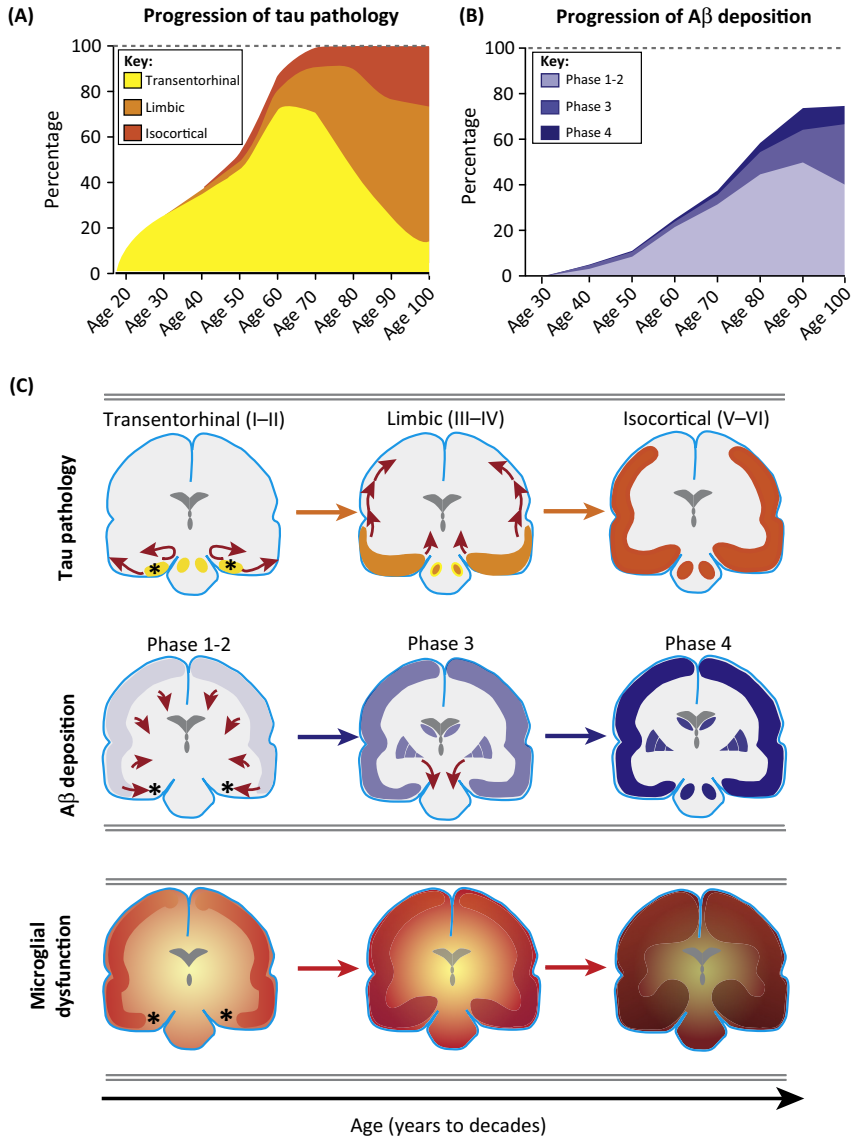

Figure 1. Development of Tau and Amyloid Pathologies and the Neuroinflammatory Response. (A) Early tau pathology begins in young adulthood in the transentorhinal cortex (TEC; Braak stages I–II, or the transentorhinal stage which is clinically silent). With aging, tau pathology spreads beyond the TEC and entorhinal cortex into hippocampus and allocortex (Braak stages III–IV, or the limbic stage where memory dysfunction begins). Subsequently, tau pathology spreads to connected neocortical association areas (Braak stages V–VI, or the isocortical stage where cognitive deficits are very advanced). Note that 100% of subjects have some degree of tau pathology after age 70. (B) Amyloid deposition begins later in life and may be present in cognitively normal subjects. (C) Tau pathology spreads in a caudal–rostral direction beginning in the locus ceruleus and TEC (asterisk), then progresses to limbic and isocortical stages. Amyloid pathology begins in neocortex, and expands caudally into allocortical and subcortical areas at later phases. With progression of both tau and Aβ pathologies, neuropathological studies [85] together with results from PET imaging of microglial activation using TSPO (translocator protein 18 kDa) radioligands [108–113] (Box 2), indicate that microglial responses likely track with both Aβ deposition and spread of tau pathology. Although TSPO-PET radioligands have some important limitations, they have provided unique insights concerning the neuroinflammatory component of AD in living subjects, and have highlighted the importance for such non-invasive imaging techniques to enhance our understanding of the *in vivo* timecourse of neuroinflammation in the development and progression of AD. Figure adapted from [2,4,6,85,107].

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