Pro-Con debate: Microglial activation is a non-specific reaction in AD and should not be a therapeutic target

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The most influential model of Alzheimer's disease (AD) pathophysiology, and therefore the most frequently targeted mechanisms in AD drug development, is the amyloid cascade hypothesis, which was originally derived from findings in rare autosomal dominant mutation carriers. Briefly, amyloid precursor protein (APP) is cleaved by either α-secretase, resulting in soluble non-amyloidogenic products, or β- and γ-secretases, which results in the amyloid-β (Aβ) peptide, which initially aggregates to form soluble oligomers, and subsequently insoluble fibrils, later found in the typical senile plaques. The soluble Aβ aggregates may be the main drivers of synaptic and neuronal loss, rather than the insoluble, fibrillar deposits. The importance of soluble forms of Aβ in the pathological AD cascade is underlined by the toxic effects of small peptide complexes on synapses and mitochondria. Respiratory chain defects and autophagic degradation are central mitochondria-related pathomechanisms in AD, which contribute to the release of toxic oxygen species, impair energy production and related axonal transport and interfere with calcium homeostasis. Aβ also leads to a local inflammatory response, which involves microglia clusters, upregulated acute phase proteins and other mediators of an inflammatory response. Microglia activation and neuroinflammation may be beneficial and neuroprotective in the early stages of AD, but overactivation of the cerebral immune system may be a harmful driver of neurodegeneration in later disease stages. Understanding the stage-dependent role of microglia response to AD pathology is a key prerequisite for the development of novel drugs targeting the immune system.