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The Role of APOE in microglia regulation in Neurodegeneration

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Alzheimer's disease (AD) is the most prevalent senile dementia affecting 4.5 million Americans. Neuroinflammatory changes are prominent and may significantly contribute to the pathologic process. Mononuclear phagocytes (brain resident microglia and recruited peripheral monocytes) accumulate around amyloid plaque in AD brains. However, their exact cellular identity, molecular and functional phenotypes, and their protective or destructive roles in AD are not well understood. This stems in part from the lack of a specific molecular signatures for mononuclear phagocytes, cell type-specific antibodies, and analytic tools for in situ characterization. We recently identified a unique TGFβ-dependent molecular signature of homeostatic (M0)- and APOE-dependent neurodegenerative (MGnD)-microglia in neurodegenerative mouse models including APP-PS1 mice and human AD. Mechanistically, the TREM2-APOE pathway mediates a switch from M0- to MGnD-microglia phenotype after phagocytosis of apoptotic neurons in a cell-autonomous manner. TREM2 induces APOE signaling which is a negative regulator of the transcription program in M0-microglia.Transcription regulatory network analysis identified direct effect of APOE on suppression of major microglial homeostatic regulators including TGFβ signaling and induction of disease-associated molecules which are essential for pathogenicity in neuroinflammation. Specific genetic ablation of Apoe and/orTrem2 in microglia restored their homeostatic phenotype and genetic ablation of Apoe or Trem2 in TAU (P301S) mice arrested neurodegeneration and brain atrophy. Therefore, APOE plays an important role in microglia phenotype regulation in neurodegenerative conditions, and restoration of the homeostatic microglia by targeting the APOE-signaling in microglia represents a novel immunotherapeutic approach. Taken together, our work identifies the TREM2-APOE pathway as a major regulator of microglial functional phenotype in neurodegenerative diseases and serves as a novel target to restore homeostatic microglia. These advances have major implications not only for understanding normal CNS function, but have opened up new avenues to understand the role of microglia in disease and most importantly have created the opportunity for consideration of ways in which microglial may be imaged and targeted for the treatment of disease. Since APOE ε4 is the major risk factor of the disease, we study the role of APOE ε4 in microglia regulation by employing novel tools including new mouse models and techniques to specifically target APOE in order to restore microglia-mediated protein clearance and brain function in animal models of tauopathies and AD. I will present recent advances in understanding the new molecular signature of homeostatic microglia, disease associated microglia and how microglia are regulated in health and disease.

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