The role of APOE in Microglia regulation in Neurogeneration

Oleg Butovsky

Harvard Medical School, USA

Keywords: Microgli, APOE, Neurodegeneration, Alzheimer's disease, immunomodulation, Innate Immunity

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.

This impairment triggers a progressive loss of cognitive skills such as memory and decision making. Neurodegeneration is a key aspect of a large number of diseases that come under the umbrella of "neurodegenerative diseases." Of these hundreds of different disorders, attention has so far focused mainly on just a handful, with Parkinson's disease, Huntington disease, being the most notable and Alzheimer's disease. A large proportion of the lesser-advertised diseases were essentially ignored.

Such disorders can lead to irreversible damage to the brain and neurodegeneration. While all three of the diseases manifest with different clinical characteristics, the mechanisms of disease tend to be identical at the cellular level. Parkinson's disease, for example , affects the basal ganglia in the Mind, it depletes dopamine. It results in swelling, swelling and tremors in the body's main muscles, which are common features of the disease. There are deposits of tiny protein plaques in Alzheimer's disease which damage various parts of the brain and lead to progressive memory loss. Huntington's disease is a progressive genetic disorder which affects the body's major muscles Severe restriction on the engine, and ultimately death.

Matters

Genetic mutations cause only an exceedingly low proportion (less than 5 per cent) of neurodegenerative diseases. The remainder was thought to be affected by:

- NEI researchers link age-related DNA changes to eye susceptibility
- Genetic engineering could open up opportunities for Parkinson's disease patients
- Scientists regain sight in mice by converting skin cells into luminous eye cells
- A harmful protein build-up inside the brain
- A loss of mitochondrial function which causes neurotoxic molecules to grow

Although the cause can vary, experts generally accept that the outcome is the promotion of apoptosis or programmed cell death, which is cell suicide deliberately for the purpose of Protection of other neurons nearby against poisonous substances.

Therapy

There are currently no available therapies for curing neurodegeneration. Medication will only relieve symptoms for each of the illnesses, and help improve the quality of life of patients. For example, memantine and donepezil in some people with Alzheimer's disease and Levodopa may often delay the development of dementia symptoms Increasing the amount of dopamine in the brain to help relieve some of Parkinson 's core symptoms.

Microglia are the CNS 'main immune cells, and very close to peripheral macrophages. They function as the main form of inflammatory cell in the brain and respond to pathogens and injury by being "activated"-a process by which morphology is rapidly modified, Proliferate and migrate to an infection / injury site where phagocytosis and pathogens are killed,

and damaged cells are removed. We secrete cytokines and chemokines as well as prostaglandins, NO and reactive oxygen species as part of their response which help elevate and direct the immune response. Therefore, they are instrumental in resolving the inflammatory response, By rendering anti-inflammatory cytokines like Il-10 Although the search for and elimination of pathogens is an essential and protective function, microglia has also been extensively studied for its harmful roles in neurodegenerative diseases and brain injury, such as Alzheimer's disease , Parkinson 's disease, ischemic injury, and traumatic brain injury.We've found that microglia in the adult brain is entirely dependent on Colony-Stimulating Factor 1 receptor (CSF1R) signaling for their survival, and that we can take advantage of this dependency by administering different CSF1R inhibitors that cross the blood brain barrier. CSF1R inhibitor administration results in the rapid removal of microglia from the adult brain-Within 7 days of continuous treatment ~80 percent of all microglia are removed and > 95 percent of all microglia are extracted within 21 days of continuous treatment.