Microglia and neuronal death in brain diseases

Microglia and their contribution to the pathomechanism of Alzheimer's disease

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The growing body of evidence highlights the significance of inflammatory processes in the pathomechanism of Alzheimer's disease (AD). Depending on age, disease stage, and other environmental conditions, neuroinflammatory processes may be beneficial, promoting neuroprotection and neuroregeneration, or can result in neuronal damage. Microglia, resident immune cells in the brain are equipped with a set of membrane receptors and detect changes in the local environment trying to maintain brain homeostasis. However, prolonged activation of microglia in AD may evoke the sustained release of inflammatory mediators and reactive oxygen species, leading to neuroinflammation which may promote amyloid-beta (Aβ) peptide accumulation and proteinopathy, changes in gene transcription, epigenetic regulation, formation of the self-propagating alterations, and neuronal death.

The novel research tools revealed the heterogeneity of the microglial population and the complexity of microglial function/dysfunction. The transcriptome-wide analysis of human microglia indicated the age-related transcriptome changes. It was found that expression of the specific set of genes was altered in AD, was increased during aging, and was affected by APOE2 haplotype. Microglia may adopt different activation states (phenotypes) to handle specific tasks in brain tissue. Because of this phenotypic diversity, targeting microglia in AD is challenging and it is necessary to understand the specific function of each type and its contribution to the pathomechanism of AD to create the way for a new therapeutic approach.

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Microglial phagocytosis of live neurons and synapses in neurodegeneration

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Excessive microglial phagocytosis of live synapses and neurons may contribute to neurodegeneration. We find that the exposure of cell-surface sialic acid and galactose are key regulators of this phagocytosis. Activated microglia release a sialidase that desialylates microglia and neurons, activating phagocytic residues on microglia, and enabling opsonins to bind to neurons. However, microglial engulfment of neurons requires UDP release from neurons activating the P2Y6 receptor on neurons. Knockout of the P2Y6 receptor in mice prevents microglial phagocytosis of live neurons, as well as neuronal and memory loss in mouse models of neuroinflammation, amyloidosis and tauopathy.

Allendorf DH, Puigdellívol M, Brown GC. (2020). Activated microglia desialylate their surface, stimulating complement receptor 3-mediated phagocytosis of neurons. Glia, 68, 989–998.
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Extracellular tau-induced microglia-mediated neuronal death

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Structural and compartmental changes of tau are being thought to be involved in various tauopaties, including frontotemporal dementia, Pick's disease, etc. Recently it has been shown that extracellularly secreted tau can be more toxic than intraneuronal but the mechanisms of this type of tau-induced

neurotoxicity are unclear. In this talk, I'll compare neurotoxic effects of various isoforms of extracellular tau and give some insights into molecular pathways how extracellular tau interacts with microglia causing neuronal loss.

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