Neuroinflammatory Processes in the Pathogenesis of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disease of the brain that is characterized by memory impairment and cognitive dysfunction. Pathological features of the disease include the extracellular deposition of amyloid beta (Aβ) peptide as plaques and the intraneuronal accumulation of hyperphosphorylated tau protein as neurofibrillary tangles. The accumulation of these proteinaceous deposits induces synaptic dysfunction, oxidative damage and neuroinflammation, resulting in neurodegeneration. Microglia and astrocytes, the brain-resident glial cells are involved in maintaining a homeostatic environment in the brain. Accumulation of amyloid plaques and the death of neurons perturbs this homeostatic environment, eliciting reiterative cycles of neuroinflammation. The inflammatory reaction, triggered by the glial cell response to Aβ, exacerbates the toxic milieu in the AD brain and contributes to further Aβ genesis. Evidence now suggests that, in the later stages of the disease, activated astrocytes contribute to amyloid load in the brain. This is in stark contrast to their role in the early stages of the disease where they are involved in the degradation and removal of amyloid plaques. Additionally, microglia, the brain-resident phagocytes that are tasked with clearing pathogens and cellular debris, also become activated in the presence of soluble Aβ and contribute to its clearance in the early stages of the disease. Employing the 5xFAD mouse model of Alzheimer's, we provide evidence that microglia contribute to amyloid plaque burden in the 5xFAD mouse brain. In addition, we discuss evidence that suggests pathways that fuel astrocytic activity in the 5xFAD mouse brain. Our results highlight the toxic environment in the Alzheimer brain that provide a neuroinflammatory landscape during disease progression.

Recent Publications

1. Paasila PJ, Fok SYY, Flores-Rodriguez N, Sajjan S, Svahn AJ, Dennis CV, Holsinger RMD, Kril JJ, Becker TS, Banati RB, Sutherland GT and Graeber MB. (2021) Ground state depletion microscopy as a tool for studying microglia-synapse interactions. Journal of Neuroscience Research 99(6):1515-1532.
2. Pratap AA and Holsinger RMD. (2020) Altered brain leptin and leptin receptor expression in the 5XFAD mouse model of Alzheimer's disease. Pharmaceuticals, 31(11):401.
3. Gaukås NH, Huynh Q-S, Pratap AA, Einarsrud M-A, Grande T, Holsinger RMD* and Glaum J*. (2020) In vitro biocompatibility of piezoelectric K0.5Na0.5NbO3 thin films on platinized silicon substrates. ACS Applied BioMaterials 3(12):8714-8721.
4. Pratap AA and Holsinger RMD. (2020) Altered brain adiponectin receptor expression in the 5XFAD mouse model of Alzheimer's disease. Pharmaceuticals, 13(7):150.
5. Porto, RR, Dutra, FD, Crestani, AP, Holsinger, RMD, Quillfeldt, JA, de Bittencourt Jr, PI, de Oliveira Alvares, L. (2018). HSP70 Facilitates Memory Consolidation of Fear Conditioning through MAPK Pathway in the Hippocampus. Neuroscience, 375:108-118.
6. Wang R and Holsinger RMD (2018). Exercise-induced brain-derived neurotrophic factor expression: Therapeutic implications for Alzheimer's dementia. Ageing Research Reviews 48:109-121.



Biography

Dr Holsinger is a Senior Lecturer in Neuroscience and Director of the Laboratory of Molecular Neuroscience and Dementia at The Brain and Mind Centre at The University of Sydney, Australia. Dr Holsinger's research interests are aimed at understanding molecular mechanisms underlying neurodegenerative diseases with a particular focus on Alzheimer's disease and the β-secretase cleaving enzyme (BACE1). This enzyme initiates the generation of amyloid-beta (Aβ), accumulation of which leads to its deposition as amyloid plaques, a pathological feature of Alzheimer's. Following seminal discoveries of increased BACE1 in the brain and cerebrospinal fluid of Alzheimer's subjects, the laboratory focuses on identifying mechanisms that lead to increased levels of BACE1 and those that regulate its transcription. His research also focuses on neurotrophic factors, in particular, brain-derived neurotrophic factor (BDNF) and its expression in the diseased brain with an aim to regulating levels of these factors for therapeutic benefit.

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