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Investigating signaling and microbial changes in Sporadic Alzheimer's disease in Humans and neuroinflammation in PolyI:C murine model

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Alzheimer's disease (AD) is the primary cause of cognitive deficit in elderly humans. Late-onset AD (LOAD) is sporadic, multifactorial, non-Mendelian accounting at present for 95% of the cases in contrast to the genetic form. There is increasing evidence that lifestyle and environmental stress such as infection and chronic inflammation are underlying culprits of neurodegenerative dementia. With impairment in smell loss and a long pre-symptomatic phase, where amyloid and Tau start accumulating causing memory loss, it is imperative to understand early molecular dysfunction and identify suitable windows for preventing the neurodegenerative process.

In a mission to resolve the etiology of AD, for finding suitable therapeutics, during my doctoral thesis, I studied the role of systemic inflammation in AD pathogenesis in a peripheral infection PolyI:C mouse model. Using molecular and imaging techniques I found that systemic viral like infection during prenatal and early postnatal life initiates chronic systemic and central inflammation and a progressive mixed vascular-AD like phenotype including depositions of amyloid beta aggregates and tauopathy, with microglia cells adopting amoeboid like phenotype accompanied by smell and memory deficits; indicating systemic inflammation contributes to AD pathophysiology and chronic inflammation as a risk factor for dementia. Parallelly the transcriptome was validated in the human AD & Vascular demented hippocampal specimens.

My work also included working on human saliva as a diagnostic non-invasive fluid in classifying dementia progression using microbial and immune signatures. In this published human study, we identified dysbiosis in some key periodontal pathogens along with changes in inflammatory markers with the progression of dementia. As smell loss is considered a prodromal sign of dementia and notch signaling is involved in olfactory information processing, I also studied and published changes in the Notch signaling pathway across stags of dementia and discovered a decrease in corpora amylacea granular bodies from the olfactory nerve specimens of patients with AD.

Taken together, my findings suggest the role of chronic inflammation as a risk factor for dementia and the possible host-pathogen interactions and signaling changes in the development or progression of AD pathology.

Jury:
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