MESEPAD

Mechanisms of sex-specific vulnerability of Parvalbumin interneurons in early Alzheimer's disease

Alzheimer's disease (AD), the main cause of dementia in the aging population, has not an effective treatment that stops or ameliorates clinical symptoms. AD affects disproportionately more women than men (proportion 2:1), but the cellular and pathogenic mechanisms that contribute to sex differences leading to higher risk and progression of AD in women are still unknown. A better understanding of sex differences in biological and pathological factors affecting clinical symptoms is key for an accurate diagnosis and personalized treatments in dementia.

Several studies indicate sex differences on brain pathology during AD progression, which may con-tribute to higher risk and accelerated cognitive decline in women with mild cognitive impairment and early AD. Interestingly, sex-differences in cognition and emotion in human were associated with functional changes of parvalbumin (PV) interneurons, the most abundant inhibitory cell type in the brain. Recent studies from our consortium partners have demonstrated that PV interneurons are highly vulnerable to pathological changes during memory loss in AD. Therefore, strategies to identify the biological causes of dysfunction and degeneration of PV interneurons at early disease stages are key to fully understand the basis of sex differences in dementia.

This project is based on the idea that functional and structural changes of PV interneurons contribute to sex differences on disruption of memory-related neural circuits early in AD. The main goal of our collaborative project is to identify genetic and cellular processes in PV interneurons that cause sex differences in the disease. To achieve this goal, we have joined efforts from leading experts in clinical and experimental research in AD and neurodegeneration to unravel changes of PV interneurons by applying cutting-edge techniques- such as single- and cell-specific transcriptomics, brain activity recordings, targeted gene editing- on human neurons from AD patients and advanced AD mouse models. In addition, we will combine our experimental findings with clinical and biomarkers data from two well-established AD patient cohorts. At the end, we aim to gain a deeper understanding of the contribution of PV interneurons on the sex differences during AD pathophysiology, which will be critical to design sex-related strategies for precise diagnosis and therapies in dementia.

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