A multi-omic analysis reveals gender-specific D-serine signatures in Alzheimer's disease

SpT-22-2

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Alzheimer's disease (AD), affecting millions worldwide, remains a significant barrier to healthy aging and is the predominant cause of dementia. Despite AD neuropathology has been well defined, the underlying causes of the disease remain debatable. Recently, sex and gender are emerging as crucial drivers of development and progression of AD dementia. So, using an integrated omics approach, this study investigated gender-related alterations in the molecular composition of postmortem hippocampus samples of healthy individuals (CTR) and AD patients.
Comparative analyses spotlighted the gender-dependent omic changes, revealing profound differences in energetic metabolism, cytoskeleton organization, and oxidative stress response (previously published in Maffioli et al. (2022) Cell Rep 40(10):111271). A marked decrease in insulin response is evident in AD females compared to males, indicating a potential vulnerability for targeted therapeutic strategies. Moreover, serine metabolism, closely tied to the glycolytic pathway and the production of the N-methyl-D-aspartate (NMDA) receptor co-agonists D-serine (D-Ser) and Glycine (Gly), is modulated across genders. The D-Ser/total serine ratio emerged as a critical factor to counteract age-related cognitive decline: in females it is mainly due to Ser metabolism upregulation, while in males it is linked to Pro/Arg metabolism. Our data support the evidence that altered L-Ser level may contribute to damaged neurotransmission and synaptic plasticity in aging and in AD patients (triggering an increase in brain D-Ser availability) and highlight how different pathophysiological mechanisms are active across genders.
This project was founded by “PRIN-2017 - Dissecting serine metabolism in the brain”.