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Understanding the Biomarkers of Alzheimer's Disease – Insights into the Development of Diagnostics and Therapeutics

Nancy Y. IP

Division of Life Science and State Key Laboratory of Molecular Neuroscience,

The Hong Kong University of Science and Technology, Hong Kong SAR;

Hong Kong Center for Neurodegenerative Diseases, Hong Kong SAR

Email: boip@ust.hk

Alzheimer's disease (AD) is the most common form of dementia and a leading cause of death among the elderly. The exact causes of AD remain unclear, making it difficult to develop effective diagnostics and treatments. There is an urgent need for reliable biomarker-based tests for the early and accurate diagnosis of AD. In response, we conducted a thorough analysis of blood proteins in AD patients and identified hundreds of biomarkers that form the "blood protein signature of AD." Furthermore, we developed a blood-based biomarker test for early detection and monitoring of AD progression. This test accurately reflects the progression of brain amyloid pathology, which is crucial for screening patients for new disease-modifying therapies for AD. Overall, our study provides a comprehensive profile of the AD plasma proteome and demonstrates the potential of a blood-based biomarker assay for the early detection and staging of AD. The discovery of blood-based biomarkers for AD is essential not only for diagnosis but also for developing intervention strategies. We previously showed that activation of the cytokine interleukin 33 (IL-33) and its receptor ST2 mitigates AD pathology by promoting microglial clearance of amyloid-beta. Our recent findings elucidate how IL-33/ST2 signaling is disrupted in AD, specifically noting that blood levels of the decoy receptor soluble ST2 (sST2) are elevated in AD patients. This increase in sST2 level is modulated by genetic factors; further analysis revealed an association between carrying a genetic variant and lower blood sST2 levels, reduced AD risk, and ameliorated AD-related endophenotypes. We evaluated the potential of sST2 as a drug target and its mechanisms using various approaches, including the development of a specific knockout mouse model for sST2. Collectively, these findings highlight the role of dysregulated IL-33/ST2 signaling in AD pathogenesis, paving the way for new therapeutic strategies.

Together, these integrative findings support a model of PD pathogenesis driven by immune dysregulation in the central nervous system involving adaptive immunity and innate myeloid neuroinflammatory responses. This work provides a foundation for mechanistically guided therapeutic strategies targeting early immune processes in both prodromal and established PD.