SOLID

Risk factors and markers for early detection of Alzheimer's Disease: focus on early-life adversity, inflammation and lipid mediators

Finding suitable and easily measurable early biomarkers for neurodegeneration and cognitive dysfunction represents the next frontier for prevention and early intervention strategies in diseases like Alzheimer's Disease (AD).

Our collective work in preclinical models has demonstrated that early-life adversity, such as stress or poor nutrition, can increase AD vulnerability, aggravate neuropathology and accelerate cognitive dysfunction. Neuroinflammation (driven by the brain's primary immune cells, microglia) has been increasingly acknowledged as an important player in AD pathology and early-life adversity primes microglia, rendering them more sensitive to subsequent challenges.

In addition, polyunsaturated fatty acids (PUFAs) and their derivatives play a key role in modulating microglia. N-3 PUFA (omega-3) metabolism is altered by early-life adversity and, recently, specialized pro-resolving mediators (SPMs; derivatives of omega-3) have been found to be altered in post-mortem AD brains. Finally, inflammation and metabolism are tightly connected in the context of early-life adversity and AD, presenting an opportunity to use metabolic sensors as potential biomarkers of (neuro)inflammation. We thus propose a translational project that will leverage data and bio-samples from four established human cohorts as well as more than 10 established in vivo and in vitro mouse and rat preclinical models. We will use these to identify early biomarkers of neurodegeneration and establish the causal role of and detailed mechanisms for early-life adversity and omega-3 in microglial priming in increasing the risk of neurodegeneration and AD.

SOLID will complete a discovery program in humans aimed at identifying early biomarkers of neurodegeneration and cognitive decline. The second, parallel, work program will be to back-translate candidate and newly identified biomarkers to validated animal models of cognitive decline and AD and test the temporal and causal relationship of these biomarkers to the central neuroinflammatory changes. We will use several innovative approaches including microglial functional assays, microglia depletion strategies, omega-3 and SPM assessment, organotypic slice cultures, and transgenic rodent models; testing the causal role of early-life adversity, omega-3 and microglia. The third work program will test the potential for early supplementation with omega-3 to protect against early-life adversity induced aggravation of neurodegeneration in AD mice and against cognitive deficits in a healthy aging human population. On completion of this proposal, we will have identified i) unique profiles of early biomarkers (cytokines, PUFAs, SPMs and metabolic sensors) predictive of cognitive dysfunction and neurodegeneration; ii) the causal role of early-life adversity in predisposition to AD; and iii) an omega-3 and SPM strategy for alleviating these effects.

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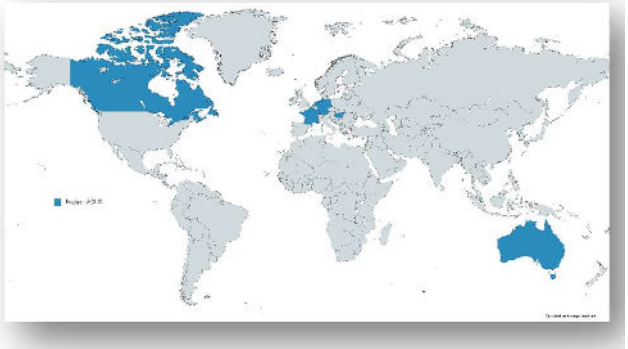

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