

Identification of dietary modulators of cognitive function in ageing using metabolomics discovery

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With a global rise in ageing population and age-associated diseases, understanding how diet modifies cognitive ageing represents key revenues for prevention. Epidemiology suggests inverse associations between specific dietary patterns (i.e. Mediterranean diet) and cognitive decline and neurodegenerative diseases [1-3]- which raises an important question: which dietary bioactives (i.e. metabolites derived from plant foods) are capable of modulating neuronal ageing?

In this discovery (D-CogPlast⁶) study, we aim to identify a combination of diet-derived metabolites associated with cognitive decline using untargeted metabolomics. We leveraged the Three-City (3C) study (a large French cohort of elderly people) and compared the metabolic profiles of 209 individuals who later developed cognitive decline over 13 years against 209 controls with preserved cognition. Subjects were matched for age at baseline, gender and level of education. Serum samples (collected at the beginning of the cohort study when all participants were cognitively healthy) were profiled using high-resolution UHPLC-QToF (Bruker Impact II) and raw UHPLC-MS data were processed using Galaxy (WorkFlow4Metabolomics.org). Validated PLS-DA clearly distinguished between case and control populations. To account for the matched case-control study design and for potential confounders (i.e. season of blood sampling, body mass index, and number of medications consumed), sparse conditional logistic regression (with bootstrapped re-sampling) was adapted. 17 ions were representative of a serum metabolomic profile associated with cognition. These ions and their clusters whose intensities were significantly elevated in each of the population groups were annotated using online and in-house databases, literature search and commercial standards. Tandem MS/MS fragmentation is presently in progress for further validation of these ions' identification.

Next, the robustness of this set of ions will be validated in a separate cohort of 400 subjects. The ability of these ions predictive of cognitive decline to modulate brain plasticity and neuronal integrity will be further investigated in an *in vitro* parabiosis assay and finally in a proof-of-principle dietary intervention mouse model. It is expected that these identified and validated biomarkers will lead to dietary intervention and recommendations for cognitive decline prevention.

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References

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