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MOLECULAR AND CELL BIOLOGY

Interplay of the human exposome, metabolome and gut microbiome in dementia and major depression

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Abstract

Background: The pathogenesis of dementia and depression is complex involving the interplay of genetic and environmental risk factors including diet, life-style and the gut microbiome. Dementia and depression co-occur and metabolomics studies may shed light on the interplay of the various risk factors.

Methods: We have studied the metabolome of 118,466 individuals including 8462 cases with a history of major depression (MDD) and 1,364 patients who developed dementia during follow-up from the UK Biobank (UKB). The human metabolome was profiled using the Nightingale platform.

Result: For both disorders, we find direct evidence that metabolites involved in the tricarboxylic acid (TCA) cycle are altered in patients, albeit that different metabolites emerge as the most significant drivers in the two disorders. Both dementia and MDD dementia patients show a marked change in the HDL/VLDL axis in blood, with similar changes in particular small and extra large HDL subfractions seen in patients with MDD and those who develop depression in the future. The two patients groups further show similar changes in fat metabolism as measured by omega 3, omega 6 and PUFA levels. When comparing metabolic profiles over environmental risk factors for MDD and dementia, we find that MDD clusters with dementia risk factors physical activity, history of previous smoking and social isolation. Integrating the metabolic profiles of major depression and the gut microbiome we find that the gut microbiome may be a key mediator in the relationship between various metabolites involved in the HDL subfractions associated to both MDD and dementia.

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Conclusion: Our study shows that energy and fat metabolism is disturbed in patients with MDD as well as patients who develop dementia in the future and that the interplay between the genome, exposome, gut microbiome, human metabolome may play role in the co-occurrence of major depression and dementia.