Scientific Meeting
AuPS | ASB
HOBART · 2022

Abstract: 53S

Hypothalamic Neurofibrosis: A New Player in the Fight Against Metabolic Disease

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Metabolic diseases such as obesity and Type-2 diabetes are characterised by insulin resistance. Cells within the arcuate nucleus of the hypothalamus (ARC) become insulin resistant and are a key regulator of metabolic dysfunction but the mechanisms are incompletely understood. Here, we identify a specialised chondroitin sulfate proteoglycan extracellular matrix (CSPG-ECM) that encapsulates neuronal populations in the ARC. Remodelling of the CSPG-ECM during the progression of metabolic diseases drives neurofibrosis, insulin resistance and metabolic dysfunction. We show that decreased CSPG-ECM turnover in the ARC is a hallmark of obesity and other metabolic diseases. Enzymatic- or small molecule-induced disassembly of CSPG-ECM within the ARC of obese/insulin-resistant mice enhances insulin infiltration into the brain, promoting the remission of neuronal insulin resistance and improved metabolic health. Our study identifies neurofibrosis as a fundamental mechanism underlying the development of obesity and insulin resistance and presents a therapeutic strategy for treating metabolic diseases.