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Innate immune cGAS/STING in HFD-induced obesity, prediabetes, and cognitive impairment

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Abstract

Background: Increasing in parallel with the worldwide aging population are rates of cognitive impairment and dementia, including Alzheimer's Disease and Alzheimer's Disease Related-Dementia. Understanding underlying mechanisms that promote cognitive impairment with aging is therefore critical. One factor that significantly increases the risk of cognitive impairment and is reaching pandemic levels is obesity and prediabetes/diabetes. Common mechanisms that could underly the relationship between obesity and prediabetes/diabetes with cognitive impairment are changes in immune system function, particularly microglial dependent changes. Specifically, the innate immune cGAS/STING pathway is implicated in both cognitive impairment and obesity and prediabetes/diabetes.

Method: 1 yr old BL6 male mice were fed 60% HFD (high fat diet) or 10% SD (standard diet) for 13 weeks. Body weight and glucose tolerance were used to determine metabolic phenotype. Cognition was measured using social recognition and fear conditioning. Hippocampal inflammatory gene expression was determined using Nanostring nCounter and cGAS/STING specific protein expression using western blotting. Additionally, we induced a prediabetic phenotype in a human microglial cell line by treating microglia for 24 hr with either palmitate alone or a combination of insulin and palmitate. Cells were then assessed for cGAS/STING protein expression using western blotting.

Result: HFD feeding resulted in increased weights and impaired glucose tolerance along with cognitive deficits. Hippocampal gene expression profiles showed changes in several genes, such as cGAS, STAT2, and IL-6 and there were changes in hippocampal cGAS/STING proteins in HFD mice. In microglia, prediabetic conditions increased expression of multiple cGAS/STING proteins, along with the immunosenescence marker p21.

Conclusion: Changes in inflammatory profiles indicate that HFD dysregulates hippocampal inflammatory gene expression and cGAS/STING protein expression in obese prediabetic mice with cognitive impairment. Microglial cGAS/STING changes indicate that this cell type is particularly sensitive to prediabetic conditions and may promote premature immunosenescence. While more data are needed to fully understand

cGAS/STING mediated microglial mechanisms of cognitive decline in obesity and pre-diabetes, these data support the hypothesis that inflammatory mechanisms are an important contributor and that the cGAS/STING pathway represents a potential target for future research.