Not Just Appetite: Obesity in Down Syndrome is a Trisomy-Driven Inflammatory Stress State.

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Résumé

Introduction

Down syndrome (DS) is associated with a high prevalence of obesity from early life, yet the underlying biological mechanisms remain poorly understood. In the general population, obesity primarily arises from dysregulated hypothalamic control of appetite and energy balance. However, it's unclear whether obesity in DS follows similar neuronal pathways or results from trisomy-specific metabolic stress. Understanding obesity in DS is critical given the substantial variability in BMI and metabolic health among individuals.

In the brain, the hypothalamus stands as a central hub for the regulation of energy homeostasis. Unlike most other brain regions, it possesses a direct anatomical and functional connection with the systemic circulation. This strategic positioning enables the hypothalamus to integrate peripheral cues and orchestrate adaptive physiological responses, including appetite regulation, energy expenditure, and neuroendocrine signaling.

To elucidate the mechanisms driving obesity in DS, we modeled neuroinflammatory stress using iPSC-derived hypothalamic neurons from euploid individuals. By comparing transcriptomic profiles between DS and non-DS individuals across varying BMI and obesity statuses, we aim to identify trisomy-specific alterations in hypothalamic function and their potential contribution to metabolic dysregulation in DS.

Methods

iPSC lines (n=6) derived from euploid control individuals were differentiated into induced hypothalamic neurons (iHTNs) following a well-established 40-day protocol involving dual SMAD inhibition, Shh-mediated ventral diencephalic patterning, and DAPT-induced maturation. To model acute neuroinflammatory stress, Day 40 iHTNs were treated with IL-1β (10 ng/mL) for 3 hours and analyzed via bulk RNA sequencing. The resulting transcriptomic signatures were compared against two independent cohorts: (1) DS-iHTNs from the

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GO-DS21 project, stratified by donor BMI (high BMI: > 35 vs. low BMI), and (2) published transcriptomic profiles from super-obese and control iHTNs from non-DS euploid donors.

Results

Transcriptomic profiling of control iHTNs exposed to IL-1β revealed a robust induction of pro-inflammatory signaling, including TNF, IL-17, JAK-STAT, and NF-B pathways. Surprisingly, the transcriptomic signature of high-BMI DS iHTNs showed limited overlap with the signatures of non-DS "super-obese" donors. Instead, high-BMI DS neurons exhibited a strong convergence with the IL-1β-treated state, characterized by the activation of cytokine, extracellular matrix, and hypoxia pathways, alongside suppressed neuroactive ligand and synaptic signaling. This inflammatory profile was further underscored by the consistent dysregulation of Human Chromosome 21 (HSA21) genes linked to immune responses, such as MX1 and MIR155HG.

Conclusions

Our findings demonstrate that obesity in DS represents a trisomy-conditioned metabolic stress state that is fundamentally distinct from canonical obesity. The striking similarity in transcriptomic signatures between high-BMI DS iHTNs and the IL-1β-treated inflammatory model rather than non-DS "super-obese" profiles suggests that DS-related obesity is driven by chronic, HSA21-mediated inflammatory signaling. These results identify immune-mediated pathways as primary therapeutic targets for managing metabolic health in the Down syndrome population.
Funding: ANR GENESIF-DS21 and EU Horizon 2020 (Grant 848077 GO-DS21)

Mots-Clés: Down syndrome, Obesity, Hypothalamic neurons, Neuroinflammation, iPSC model, Transcriptomic analysis.