DEPRESSION AND CARDIOVASCULAR RISK IN OBESITY: IMPACT OF PROPROTEIN CONVERTASE SUBTILISIN/KEXIN TYPE 9 AND BRAIN-DERIVED NEUROTROPHIC FACTOR ON ADIPOCYTES

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Introduction. Obesity, raising Worldwide, increases the susceptibility to cardiovascular diseases (CVDs) and mood disorders. Among these, depression enhances the CVD risk and it is approximately twice as prevalent in women. Obesity, depression and CVDs often come hand in hand, although a mechanistic link among these three conditions remains not well defined. Aim. To unravel molecular pathways beneath these liaisons.
Methods. In 642 obese individuals, of the cross-sectional SPHERE (Susceptibility to Particle Health Effects, miRNAs and Exosomes) study, we evaluated possible mediators of the link between depression and obesity (proprotein convertase subtilisin/kexin type 9 (PCSK9) and Brain-Derived Neurotrophic Factor (BDNF)). We have deepened the molecular mechanisms contributing to this association by taking advantage of an in vitro model of human adipocytes (SW872 cells).
Results. In the SPHERE cohort, PCSK9, a key-regulator of cholesterol, mediated 11% of the relationship between depression and insulin resistance, a CVD risk factor. This association was lost in carriers of the loss-of-function PCSK9 R46L variant, confirming a possible causal role for PCSK9 in the link between depression and insulin resistance. Since SPHERE cohort comprises obese individuals, the effects of PCSK9 on SW872 cells were investigated. The silencing of PCSK9 raised the adipocyte differentiation process. Since BDNF Val66Met human polymorphism is involved in the onset of depression, in CVD risk and in adipose tissue pathophysiology, we measured circulating BDNF levels in the SPHERE cohort. Circulating BDNF was negatively associated with depression (BDI-II score), while positively associated with insulin and HOMA-IR, an index of insulin resistance, in females. Treatment of SW872 cells with ProBDNFMet synthetic peptide impaired adipogenesis and the insulin signaling pathway.
Conclusions. PCSK9 and BDNF may share biological mechanisms underlying the association between depression and insulin resistance. This suggests how they may be intertwined in modulating CV risk factors in the presence of an obesity-driven depressive-like phenotype.

RESTRING: MANAGING FUNCTIONAL ENRICHMENT OF COMPLEX EXPERIMENTAL DESIGNS MADE EASY

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Functional enrichment analysis is an analytical method to extract biological insights from gene expression data, popularized by the ever-growing application of high-throughput techniques. Typically, expression profiles are generated for hundreds to thousands of genes/proteins from samples belonging to two experimental groups, and after ad-hoc statistical tests, researchers are left with lists of statistically significant entities, possibly lacking any unifying biological theme. Functional enrichment tackles the problem of putting overall gene expression changes into a broader biological context, based on pre-existing knowledge bases of reference: database collections of known expression regulation, relationships and molecular interactions. STRING is among the most popular tools, providing both protein-protein interaction networks and functional enrichment analysis for any given set of identifiers. For complex experimental designs, manually retrieving, interpreting, analyzing and abridging functional enrichment results is a daunting task, usually performed by hand by the average wet-biology researcher. We have developed restring (https://github.com/Stemanz/restring), a cross-platform, open-source software that seamlessly retrieves from STRING functional enrichments from multiple user-supplied gene sets, without any need for specific bioinformatics skills. As a core capability, it aggregates all such findings into human-readable table summaries, with built-in features to easily produce user-customizable publication-grade clustermaps and bubble plots. Everything is managed through reString's straightforward graphical user interface in just a few clicks and seconds of processing times. The software is backed with a comprehensive online documentation, YouTube installation tutorials, sample input files, online support, an upcoming publication and more.