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Cholinergic microRNA-132 sheds new light on the links between psychological stress and metabolic impairments

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Cholinergic signaling affects both anxiety-related and metabolic disorders and is continuously subjected to epigenetic and microRNA (miR) regulation. However, key anxiety-induced microRNAs may potentiate both cholinergic-mediated suppression of inflammation and metabolic syndrome-related processes. Specifically, genomic, epigenetic and microRNA regulators of acetylcholine signaling (CholinomiRs) may implement inherited and/or acquired anxiety-prone states while acting as inflammatory suppressors, which in peripheral tissues can shift the balance towards metabolic disorders. To study the *in vivo* contributions of specific cholinergic targets to miR-mediated phenotypes, we quantified their levels in diet-induced obese mice with hepatic steatosis, diverse nonalcoholic steatohepatitis (NASH) models and LDLR-/- mice, a model for familial hyperlipidemia. All of these models displayed hepatic increases of the anxiety-induced miR-132, accompanied by variable decreases in multiple miR-132 targets and lipolysis-related transcripts, and elevations in lipogenesis-related transcripts. Furthermore, engineered mice over-expressing miR-132 presented severe fatty liver phenotype, multiple miR-132 target decreases and increased body weight, serum LDL/VLDL, liver triglycerides, and prosteatotic and lipogenesis-related transcripts. Inversely, injecting diet-induced obese and LDLR-/- mice with anti-miR-132 oligonucleotides, but not knockdown of individual miR-132 targets, efficiently reversed the hepatic miR-132 excess, hepatic steatosis and hyper-lipidemic phenotype. Our findings identify miR-132 as an upstream CholinomiR regulator of both anxiety and hepatic lipid homeostasis, which displays context-dependent suppression of multiple targets with cumulative synergistic effects; and call for interrogating cholinergic impairments as co-regulating causes of anxiety-related disorders, hepatic steatosis and NASH. Furthermore, realization of the intriguing cholinergic-mediated tradeoff between anxiety and metabolic-related phenomena may offer novel opportunities for re-classifying healthy and un-healthy anxiety- and metabolic-prone states, discriminating between causes of stress-related and metabolic disorders, and cautiously identifying novel cholinergic biomarkers and management strategies.

Biography

Hermona Soreq was trained at Weizmann Institute of Science and the Rockefeller University. At Hebrew University of Jerusalem, she holds a University Slesinger Chair in Molecular Neuroscience and is also a founding member of the Edmond and Lily Safra Center for Brain Science. Her research pioneered the application of molecular biology and genomics to the study of cholinergic signaling, with a recent focus on its microRNA regulation and on signaling changes in health and in nervous system and metabolic disease. She is the elected Head of International Organization of Cholinergic Mechanisms, served as elected Dean of Hebrew University's Faculty of Science from 2005-2008, authored hundreds of publications and won numerous awards in Israel.

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