Frank Madeo (ORCID: 0000-0002-5070-1329): Molecular characterization of spermidine signaling

Research interest and scientific background: Spermidine, like other polyamines, is produced in many organisms and strongly modulates physiological processes including aging and immunity. Polyamines are studied intensively with respect to their function in transcriptional regulation, post-translational modifications, in eukaryotic and prokaryotic translation and RNA modulation. This research project addresses how spermidine metabolism influences the acetyl-CoA flux and histone acetylation. Our group showed that high acetyl-CoA levels promote acetylation of histones and cytosolic proteins, leading to repression of autophagy genes and reducing lifespan (1). Spermidine/Spermine N(1)-acetyltransferase 1 (SSAT1) consumes cellular acetyl-CoA as it acetylates spermidine and spermine to facilitate their secretion (2). We therefore hypothesize, that the levels of acetyl-CoA and spermidine regulate histone acetylation, autophagy and lifespan in a "Yin-Yang" relation.

Approach and methods The student will genetically modulate cellular levels of SSAT1 in yeast and flies and determine whether spermidine still promotes histone hypoacetylation and subsequent changes in DNA methylation as well as induction of autophagy and lipophagy, since the levels of acetyl-CoA also determine lipid metabolism. Further, the student will interfere with both, intracellular acetyl-CoA production via disruption of mitochondrial acetyl-CoA hydrolase ACH1, which has been shown to result in reduced autophagy by increased levels of cytosolic acetyl-CoA and subsequent hyperacetylation of histones and spermidine levels via overexpression of ornithine decarboxylase 1 (ODC1), the rate-limiting enzyme for polyamine biosynthesis.

Affiliation: The student will work at the Institute of Molecular Biosciences at the University of Graz. This project is directly connected to the doc.fund Molecular Metabolism.

References:

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