p53 in the control of adipose tissue homeostasis

Summary

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Supervisor: PD Dr. Andreas Prokesch
Availability: This position has been occupied.
Offered by: Medical University of Graz
Application deadline: Applications are accepted between February 05, 2018 00:00 and April 02, 2018 23:59 (Europe/Zurich)

Description

Background: According to the WHO about 2 billion people are currently overweight or obese. Increased adiposity is a strong risk factor for the metabolic syndrome, a cluster of disorders including type 2 diabetes mellitus and cardiovascular diseases. Adipose tissue (AT) is a major determinant in the development of metabolic syndrome and the body's largest endocrine organ (Gesta, Tseng, & Kahn, 2007). In times of starvation, by provision of free fatty acids and glycerol as energy substrates, AT is crucial for systemic energy homeostasis (Zechner, Madeo, & Kratky, 2009). The tumor suppressor p53 is a transcription factor activated in cancerous cells by a variety of stress signals such as DNA damage, oncogene activation, nutrient deprivation, and hypoxia (Kastenhuber & Lowe, 2017). Once activated, the p53 pathway has a wide range of downstream effects among which cell death, cell cycle arrest, autophagy, and regulation of cellular metabolism are most prominent (Berkers, Maddocks, Cheung, Mor, & Vousden, 2013). While many functional aspects for the p53-mediated cellular stress response during tumorigenesis (and therefore in rapidly dividing cells) are well established, much less is known about the role of p53 in non-transformed, post-mitotic cells and tissues. We have shown an upregulation of p53 signaling by starvation in several tissues, including adipose tissue and liver (Schupp et al., 2013). In a recent publication, we have shown that p53 protein is stabilized in hepatocytes under starvation (Prokesch et al., 2017). Acute, liver-specific knock-out showed that p53 is necessary for amino acid catabolism and glucose maintenance under starvation, while in the fed state glycogen storage is reduced and lipids accumulate in hepatocytes. Hence, our work suggests that, beyond its role as tumor suppressor, p53 plays a role as metabolic regulator in normal cells and tissues. We recently acquired an FWF-DACH grant in collaboration with the Charite in Berlin (Prof. Michael Schupp) and the German Institute for Nutritional Research (Prof. Tim Schulz). In this consortium we will utilize novel tissue-specific, inducible knock-out mouse models to investigate the role of p53 in the metabolism of liver, white adipose tissue, brown adipose tissue, and skeletal muscle.

Hypothesis and Objectives: The aim is to determine the effects of p53 in AT on the acute physiological starvation response that is characterized by dynamic changes in metabolic gene expression patterns and rapid shifts of nutrient fluxes via processes such as lipolysis and lipophagy.

Methodology: The PhD candidate working in Graz will investigate AT metabolism after acute AT-specific ablation of p53, directly comparing the effects in white, brite, and brown ATs. For that, a novel mouse model (Adiponectin-CreERT2xp53flox) will be used, that will be phenotypically, histologically, and metabolically characterized in our lab. Furthermore, the candidate will work with cell lines and primary cells to decipher detailed molecular mechanisms, using classical cell culture work (protein overexpression, Crispr/cas9, RNAi, proliferation assays) followed by downstream analyses such as western blot, qPCR. Mechanisms under scrutiny will be crosstalk with other starvation-relevant pathways such as AMPK, mTOR, Sirt1, and PPAR singaling. Further, assays to investigate lipid metabolism (triglyceride hydrolase assay, assessment of lipophagy and de novo lipogenesis, etc.) as well as various omics approaches (e.g. transcriptomics, lipidomics) will be applied.

References:


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