Title of PhD thesis: Resveratrol-mediated changes on metabolism and endocrinology of adipose tissue

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Background. Obesity is a major public health problem in developed countries. The abnormal increase in body fat is accompanied by an increased morbidity and mortality (1). An appreciated feature of expanding adipose tissue is localized hypoxia and inflammation. Via its secretion products, adipose tissue itself participates in the development of obesity-related disorders including cardiovascular disease and type 2 diabetes mellitus. Classical interventions such as diet and physical exercise often fail; therefore extensive research is performed to identify new therapeutic targets. Recently resveratrol, a natural plant product present in grapes and red wine gained attention due to its anti-cancer, anti-inflammatory, and anti-obesity effects (3-5). However, the molecular mechanisms by which resveratrol exerts its effects, especially in adipose tissue, are not entirely known. Although increasing evidence indicates that resveratrol may protect against diet-induced obesity by activating the deacetylase Sirt1 (6, 7), a number of reports also indicate Sirt1-independent effects.

Previous data. Dr. Fischer-Posovszky studies the effects of resveratrol in human adipocytes. Her data indicate that resveratrol may antagonize the development of obesity and its related co-morbidities (8). She identified a novel pro-apoptotic function of resveratrol, which sensitized fat cells for TRAIL-induced apoptosis in a Sirt1-independent manner (9). Prof. Kietzmann studies the effects of resveratrol in conjunction with hypoxia-dependent gene expression in the liver, especially hepatocytes. He demonstrated that resveratrol influences carbohydrate metabolism in the liver and blood glucose homeostasis. The interaction between the two transcriptional regulators FoxO1 and HNF-4 were of crucial importance (10).

Objective. The overall goal of this study is to assess whether resveratrol or its target molecule Sirt1 are suitable for the prevention and treatment of obesity and its related co-morbidities. Specifically, we aim to identify the molecular mechanisms by which resveratrol acts on fat cell metabolism and the expression and secretion of endocrine mediators.

Project description. The human preadipocyte cell line SGBS (11) will be used as model system to study resveratrol-mediated effects on fat cell metabolism and endocrine function. Our published data show that resveratrol enhances insulin-stimulated glucose uptake, but inhibited synthesis of triglycerides from glucose (8). We hypothesize that resveratrol stimulates glucose utilization within the cell especially by activating oxidative phosphorylation. Since oxidative phosphorylation may be modified by the oxygen tension and due to the fact that the action of insulin involves hypoxia-inducible factors (9), these glucose utilizing pathways will be assessed in established assay systems under normoxic and hypoxic conditions. Expression of OXPHOS genes, mitochondrial biogenesis and activity are monitored in parallel. Resveratrol-mediated effects on genes for secreted endocrine mediators will be studied by qPCR and Luminex technology. The role of Sirt1 will be addressed by pharmacological (sirtinol, nicotinamide) and genetic (shRNA) inhibition (8, 9). Sirt1 is a deacetylase acting on transcription factors and/or their co-activators; therefore co-immuno- and chromatin-immunoprecipitations (ChIP) will be used to indentify downstream-targets of Sirt1. The in vitro findings will be confirmed in an animal model established in the Kietzmann group; male Wistar rats receive i.p. injections with resveratrol at a dose of 5 or 10 mg/kg/day for 2 days (10). Blood samples are collected for measuring insulin sensitivity and serum adipokine levels. Epididymal and inguinal adipose tissues are collected for gene expression and functional studies. Adipocytes are obtained by collagenase digestion and used for metabolic studies ex vivo.
References: