Metabolic signature of post-fasting processes

Summary

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Supervisor:	Prof. Dr. Frank Madeo
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between February 04, 2019 00:00 and March 31, 2019 23:59 (Europe/Zurich)

Description

Background:

The pharmacological induction of autophagy has emerged as a feasible strategy to mimic at least some of protective effects of fasting against aging (1). Using a screening approach for the systematic identification of potential anti-aging agents, the Madeo laboratory was able to identify a natural polyphenol (flavonoid subgroup) that promotes lifespan and induces autophagy in yeast, worms, flies, and cultivated human cells (manuscript in revision). Polyphenols are a group of plant secondary metabolites that have been associated with several health benefits (2).

Hypothesis and objective:

Several natural autophagy inducers like spermidine and the polyphenol resveratrol exert beneficial effects during aging, for instance cardioprotection in rodents (3, 4). We thus hypothesize that our newly identified polyphenol, a natural autophagy inducer with lifespan-extending potential, may also exert protective effects in mice. Therefore, we aim at determining whether the polyphenol has a favorable impact on mouse organs (heart, liver) and if yes, whether this is autophagy-dependent.

Methods:

The DK-MCD student will use intraperitoneal injection of the polyphenol or DMSO to assess autophagy induction in the hearts and livers of mice. To assess possible cardioprotection, infarct size after prolonged myocardial ischemia in mice as well as e.g. cardiac hypertrophy and diastolic function in old mice after polyphenol treatment will be evaluated. In addition, the student will measure the mechano-elastical properties of cardiomyocytes in vivo and determine sub-clinical inflammation rates. Moreover, a rat model for hypertension-induced congestive heart failure will be employed to analyze e.g. systemic blood pressure, cardiac hypertrophy and diastolic function. To assess liver protection, hepatic damage after ethanol intoxication by quantifying alanine aminotransferase activity in polyphenol-treated and untreated mice will be measured. If positive results are obtained, the student will test (in mice) whether polyphenol-mediated cardioprotection/hepatoprotection is dependent on autophagy (using Atg5-deficient mice).

This project should lead to the *in vivo* characterization of autophagy-dependent cardio- and/or hepatoprotective effects of our identified polyphenol.

The results of this work will facilitate the verification of the adequate fasting timeframe to maximize its metabolic effect and thus effectivity. Furthermore, different fasting strategies may be compared by determining their metabolic profile.

References:

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2. Mattson MP, Longo VD, Harvie M (2017) Impact of intermittent fasting on health and disease processes. Ageing Res Rev. 39:46-58. doi: 10.1016/j.arr.2016.10.005
3. Fontana L, Partridge L (2015) Promoting health and longevity through diet: from model organisms to humans. Cell. 161(1):106-18. doi: 10.1016/j.cell.2015.02.020
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5. Tinsley GM, La Bounty PM (2015) Effects of intermittent fasting on body composition and clinical health markers in humans. Nutr Rev. 73(10):661-74. doi: 10.1093/nutrit/nuv041

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