Lipid hydrolysis in cancer metabolism and signaling

Summary

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Supervisor:	Prof. Dr. Ruth Birner-Gruenberger
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:

Overweight and obesity are associated with chronic diseases such as diabetes mellitus type 2, non-alcoholic fatty liver disease, atherosclerosis, musculoskeletal disorders, and cancer. Despite numerous studies, the relationship between obesity and the pathogenesis of cancer is mechanistically not understood. Increased plasma concentrations of insulin and other hormones and/or chronic inflammation may be involved. Fatty acid (FA) metabolism is poised at the junction between such pathophysiologies and the cancerous disease state as it has been recognized to play a key role in the initiation of metastasis and cancer cell proliferation. Lipid hydrolases are responsible for mobilization of FAs and production and degradation of lipids involved in cell signaling pathways and may therefore act as oncogenic regulators affecting tumor development and aggressiveness as demonstrated for monoglyceride lipase. We and others have found that adipose triglyceride lipase (ATGL), the major enzyme in triacylglycerol (TG) hydrolysis, has a tumor suppressive role (1,2). CRISPR/Cas9-mediated deletion of ATGL in A549 lung carcinoma cells revealed, in addition to the expected direct effects on TG metabolism, an increase in levels of oncogenic signaling lipids (i.e. lysophospholipids and ether lipids) and activation of SRC kinase that is linked to enhanced cell migration (1). ATGL deficiency may thus cause dysregulation of other lipid hydrolases, potentially via the transcriptional regulators PPARα and/or sirtuin1, whose activities have been shown to depend on ATGL function in heart and liver. Moreover, forced overexpression of ATGL in hepatocarcinoma cells has been shown to impose glycolytic rewiring through PPARα mediated stabilisation of the tumor suppressor p53 thereby reducing proliferation (2).

Hypothesis and objective:

We hypothesize that loss of ATGL leads to aberrant metabolism and lipid signaling, which results in aggressive cancer phenotypes. In light of these causalities, we aim to:

- investigate changes in cancer metabolism in cancer cells overexpressing or lacking ATGL activity;
- investigate p53 regulation and crosstalk of SRC and p53 in cancer cells overexpressing or lacking ATGL activity;
- characterize the lipolytic proteome and lipidome in cancer cells overexpressing or lacking ATGL activity;
- establish the links between ATGL and other dysregulated lipid hydrolases via PPARα and/or sirtuin1 activity, as well as oncogenic signaling lipids and SRC;
- determine the relative expression of lipid hydrolases in various cancer cell lines, in public transcriptomic patient datasets, and in cancer patient samples.

Methodology:

- Cell culture
- Genetic manipulation of cancer cells
- Biochemical assays
- Proteomics
- Metabolomics

References:

1. Tamara Tomin et al. Deletion of Adipose Triglyceride Lipase Links Triacylglycerol Accumulation to a More-Aggressive Phenotype in A549 Lung Carcinoma Cells. J. Proteome Res. 2018. 17:1415-1425. doi 10.1021/acs.jproteome.7b00782. http://www.ncbi.nlm.nih.gov/pubmed/29457907
2. Luca Di Leo et al. Forcing ATGL expression in hepatocarcinoma cells imposes glycolytic rewiring through PPARα/p300-mediated acetylation of p53. Oncogene 2018. doi 10.1038/s41388-018-0545-0. https://doi.org/10.1038/s41388-018-0545-0

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