# Post Translational Regulation of Sterol Regulatory Element Binding Protein (SREBP)-1 by Adipose TriGlyceride Lipase (ATGL)

## Summary

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| Supervisor: | Prof. Dr. Gerald Höfler |
| Availability: | This position is available. |
| Offered by: | Medical University of Graz |
| Application deadline: | Applications are accepted between July 15, 2019 00:00 and September 15, 2019 23:59 (Europe/Zurich) |

## Description

Background:

During the last three decades, Sterol Regulatory Element Binding Protein transcription factors (SREBPs) have been identified as master regulators of lipid homeostasis by the Goldstein and Brown laboratories (1). Their work has not only yielded a Nobel Prize in “Physiology or Medicine”, but more importantly, it saved the lives of hundreds of thousands of patients suffering from hypercholesterinemia. The SREBP isoform-1c is proteolytically activated when unsaturated(u) fatty acids(FAs) are scarce. Active SREBP-1c transactivates FA biosynthetic genes to re-establish the lipid equilibrium (2). On the other side of the metabolic spectrum, Adipose triglyceride lipase (ATGL) was found to be an essential enzyme for triacylglycerol (TAG) hydrolysis (3). During fasting, SREBP-1c mediated FA biosynthesis in the liver is stalled. At the same time, however, ATGL liberates FA from white adipose tissue (WAT) to provide a reliable source of energy for the organism (1-5).

Hypothesis and Objectives:

Our preliminary data from mice lacking ATGL suggest that FAs released from the WAT suppress proteolytic activation of SREBP-1c in the liver. We therefore hypothesize that cognate lipid messengers released by ATGL regulate fatty acid biosynthesis. Remarkably, the potential interplay between ATGL and SREBP-1c has not been studied so far. Therefore, the main objective for a prospective Ph.D. student is to dissect the mechanistic relationship between ATGL and SREBP-1c.

Methodology:

SREBP-1c regulation will be studied in livers of three different mouse models that are either, lacking ATGL systemically, in the liver or, in the WAT. These mice will be starved and re-fed a carbohydrate rich diet to activate SREBP-1c and its lipogenic target genes including, ACC-1 and FASN. Immunoblotting of fractionated cellular components, quantitative real time PCR, microscopic/physical interaction studies and molecular transport assays (5) will allow us to study in which organ ATGL is needed to suppress SREBP-1c. To further dissect molecular details of the interesting interplay of ATGL and SREBP-1c, we will use similar biochemical approaches on cultured primary hepatocytes.

Importantly, we are in an ongoing collaboration with Peter Espenshade (Johns Hopkins Medical School) a specialist on SREBP proteolytic regulation, who is a former Goldstein and Brown laboratory fellow and with the discoverer of ATGL, Rudolf Zechner (University of Graz). This allows us to combine cutting edge technologies from both, the fields of lipogenesis and lipolysis. Moreover, it will facilitate (fully funded) international student exchanges during the course of the PhD study period. Eventually the project work should help us to understand the long sought after connection between lipogenesis and lipolysis in more detail.

References

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