Structure-function relationship of lipolytic regulation

Summary

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Supervisor:	Prof. Dr. Monika Oberer
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

Research interests and scientific background:

Intracellular mobilization of triacylglycerols (TGs) depends on the consecutive action of adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and monoglyceride lipase (MGL) and their interplay with regulatory proteins. The importance of ATGL in lipolysis is emphasized by multiple mechanisms regulating its enzymatic activity including the ATGL co-activator CGI-58 (also known as ABHD5), the inhibitor G0/G1 switch protein 2 (G0S2), and the inhibitory protein hypoxia-induced lipid droplet-associated (HILPDA, also known as HIG2) (1-3). Interestingly, studies also suggest that additional TG lipases are involved in mobilization of fatty acids for lipoprotein synthesis in hepatic very low-density lipoprotein production (4). The overall objective in the Oberer group is to provide a detailed mechanistic understanding of molecular processes underlying lipid hydrolysis by biochemical and biophysical characterization of lipases and regulators. Biomolecular NMR spectroscopy and protein crystallography are employed as the main structural methods (5, 6).

Affiliation:

The student will work at the Institute of Molecular Biosciences at the University of Graz. This project is connected to the SFB Lipid Hydrolysis.

Hypothesis and objective:

The project aims to establish comprehensive structure-function relationships of mammalian lipases at the lipid-droplet water interphase. Within the SFB, the student will perform an array of studies from genetics to biochemical experiments to modelling to obtain details the hydrolytic reactions. To fully understand how the enzymatic function and regulations are realized at the molecular levels, determination of the 3D structures of the involved proteins and complexes in presence of substrates and inhibitors are required.

Experimental approaches:

The student will learn all steps necessary for structural and biochemical characterization of proteins. These include cloning, protein expression in different host organisms, protein purification, reaction kinetics, enzyme activity and inhibitor assays. The training will also include structural techniques like protein NMR spectroscopy, small angle X-ray scattering and/or protein X-ray crystallography. The student will strongly interact with other research groups within this SFB, including mass spectrometry.

References:

1. Lass A, Zimmermann R, Oberer M, Zechner R. Lipolysis - a highly regulated multi-enzyme complex mediates the catabolism of cellular fat stores. *Prog Lipid Res*. 2011; 50(1):14-27
2. Cerk IK, Wechselberger L, Oberer M. Adipose Triglyceride Lipase Regulation: An Overview. *Curr Protein Pept Sci*. 2018;19(2):221-233
3. Padmanabha Das KM, Wechselberger L, Liziczai M, De la Rosa Rodriguez M, Grabner GF, Heier C, Viertlmayr R, Radler C, Lichtenegger J, Zimmermann R, Borst JW, Zechner R, Kersten S, Oberer M. Hypoxia-inducible lipid droplet-associated protein inhibits adipose triglyceride lipase. *J Lipid Res*. 2018 Mar;59(3):531-541

4. Wu JW, Wang SP, Alvarez F, Casavant S, Gauthier N, Abed L, Soni KG, Yang G, Mitchell GA. Deficiency of liver adipose triglyceride lipase in mice causes progressive hepatic steatosis. *Hepatology*. 2011;54(1):122-32
5. Boeszoermenyi A, Nagy HM, Arthanari H, Pillip CJ, Lindermuth H, Luna RE, Wagner G, Zechner R, Zangger K, Oberer M. Structure of a CGI-58 motif provides the molecular basis of lipid droplet anchoring. *J Biol Chem*. 2015 Oct 30;290(44):26361-72
6. Aschauer P, Zimmermann R, Breinbauer R, Pavkov-Keller T, Oberer M. The crystal structure of monoacylglycerol lipase from M. tuberculosis reveals the basis for specific inhibition. *Sci Rep*. 2018 Jun 12;8(1):8948

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