# Biosynthesis of the late endosomal/lysosomal lipid bis(monoacylglycero)-phosphate

## Summary

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| Supervisor: | Prof. Dr. Robert Zimmermann |
| 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

Research interests and scientific background:

Bis(monoacylglycerol)phosphate (BMP), also known as lysobisphosphatidic acid (LBPA), is a phospholipid found in intraluminal vesicles of late endosomes/lysosomes. BMP facilitates the formation of intraluminal vesicles in acidic organelles (1) and plays a key role in lipid degradation (2). It is capable of stimulating the activity of lipid hydrolases and lipid-binding/transfer proteins and thereby promotes lysosomal degradation and sorting of lipids. Its concentration in tissues and serum drastically increase in genetic and drug-induced lysosomal storage disorders (2). Despite the central role of BMP in lipid sorting and its association with lysosomal dysfunction, little is known about enzymes catalyzing BMP synthesis and degradation. Recently, we identified ABHD6 as BMP-degrading enzyme (3). The goal of this project is to obtain basic insights into the molecular pathways regulating BMP synthesis.

Affiliation:

This project is part of the SFB Lipid Hydrolysis. The experimental work will be done at the Institute of Molecular Biosciences (IMB) at the University of Graz, where lipid metabolism is a major topic of several research groups. Special expertise is available for gene cloning, protein expression, enzyme characterization, cell and tissue culture techniques, lipid analysis, and for the generation and characterization of mutant mice.

Hypothesis and objective:

Our central aim is to identify enzymes catalyzing BMP synthesis and to investigate the consequences of defective BMP synthesis on lysosomal function *in vitro* and *in vivo*. We hypothesize that defective BMP synthesis strongly affects lysosomal lipid degradation pathways and possibly causes lysosomal storage disease. We expect that exploring the molecular basics of BMP metabolism will unveil metabolic relationships essential for the understanding of lipid degradation in acidic organelles and lysosomal dysfunction.

Experimental approaches:

To identify and characterize BMP-synthesizing enzymes, the student will perform the following experiments:

- Cloning, overexpression, and purification of candidate enzymes: We have established expression systems for bacteria, yeast, insect cells, and mammalian cells.
- Detection of enzyme activity: The activity of candidate enzymes will be characterized in established acyltransferase/transacylase assays. Lipid products will be analyzed using liquid chromatography-mass spectrometry or by thin layer chromatography using radiolabeled lipid metabolites.
- Characterization of cells with defective BMP synthesis: Enzymes catalyzing BMP-synthesis will be silenced in mammalian cells using shRNA or CRISPR. Changes in the concentrations of BMP and other lipids will be detected using liquid chromatography-mass spectrometry. Changes in late endosomal/lysosomal morphology will be detected using laser scanning or electron microscopy
- *In vivo* characterization of mice with defective BMP synthesis: The student will utilize BMP synthase-deficient mouse models as *in vivo* model to investigate the consequences on lysosomal and overall lipid and energy me-

tabolism. Basic characterization of mutant mice will include the determination of growth, fertility, body composition, locomotor activity, substrate usage, and energy expenditure. Changes in BMP and other lipids in tissues and plasma will be determined by liquid chromatography-mass spectrometry. To investigate late endosomal/lysosomal function, tissue sections will be stained for specific markers for late endosomes/lysosomes and lipids.

References:


1. Matsuo H, Chevallier J, Mayran N, Le Blanc I, Ferguson C, Fauré J, Blanc NS, Matile S, Dubochet J, Sadoul R, Parton RG, Vilbois F, Gruenberg J. Role of LBPA and Alix in multivesicular liposome formation and endosome organization. Science. 2004; 303: 531-4. doi: 10.1126/science.1092425
2. Gallala HD, Sandhoff K. Biological function of the cellular lipid BMP-BMP as a key activator for cholesterol sorting and membrane digestion. Neurochem Res. 2011; 36: 1594-600. doi: 10.1007/s11064-010-0337-6
3. Pribasnig MA, Mrak I, Grabner GF, Taschler U, Knittelfelder O, Scherz B, Eichmann TO, Heier C, Grumet L, Kowaliuk J, Romauch M, Holler S, Anderl F, Wolinski H, Lass A, Breinbauer R, Marsche G, Brown JM, Zimmermann R. α/β Hydrolase Domain-containing 6 (ABHD6) Degrades the Late Endosomal/Lysosomal Lipid Bis(monoacylglycero)phosphate. J Biol Chem. 2015; 290: 29869-81. doi: 10.1074/jbc.M115.669168


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