Adipose TriGlyceride Lipase (ATGL) plays an essential role in bronchiolar club cell metabolism and protects from lung cancer development

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 February 04, 2019 00:00 and March 31, 2019 23:59 (Europe/Zurich)

Description

Background:

Cellular energy homeostasis critically involves storage of triglyceride (fat) and its hydrolysis by Adipose TriGlyceride Lipase (ATGL). ATGL is the rate-limiting enzyme of intracellular fat lipolysis. ATGL-knockout mice (AKO) quickly develop deadly cardiac myopathy due to abrogated PPARα lipid signaling. Cardiac myocyte specific transgenic ATGL re-expression (cTg) in AKo/cTg mice however, leads to complete phenotypic rescue (1). Nevertheless, we recently discovered that AKo/cTg mice frequently develop lung cancer later in life (2).

One of our Ph.D. students found a possible explanation for this phenotype. Patho-histological analysis of AKO/cTg-lungs pointed to the bronchiolar epithelium as the origin of neoplastic lesions and western-immunoblotting revealed that club-cell secretory protein (CCSP) was abrogated. Bronchiolar epithelial club cells are the gatekeepers of bronchiolar homeostasis. They are essential for bronchiolar regeneration and CCSP shows important broncho-protective functions (3, 4). Interestingly, we found that club cells show a very active fat metabolism. In analogy to cardiac myocytes, club cells of AKo/cTg mice show distinct metabolic defects. Lipidomics indicated greatly increased triglyceride levels and using transmission electron microscopy we detected reduced numbers of mitochondria. Moreover, isolated club-cells from AKO/cTg mice showed impaired respiratory complex-I and -II based respiration.

The bronchiolar epithelium is subject to various physical, biological and chemical insults that are generally swiftly repaired. To test the reparative capacity of bronchii we abrogated club-cells using naphthalene (NA) (5). Interestingly, AKO/cTg club cells regenerated much slower than controls, as evidenced by immunohistochemical CyP2F2 regeneration-marker staining.

Hypothesis and Objectives:

We suggest that impaired club-cell differentiation during bronchiolar regeneration is linked to the neoplastic phenotype originally seen in AKO/cTg mice. ATGL plays a significant, however, as yet widely unappreciated role in pulmonal health.

Therefore, a prospective PhD. student should delineate the molecular and biochemical mechanism underlying the essential role of ATGL in bronchiolar club cell metabolism. She/He should test if ATGL is a potential new tumor suppressor gene in the lung.

Several pulmonary diseases including COPD and allergic asthma are linked to CCSP. Potential roles of lung lipid metabolism in asthma and COPD development are additional aims of our group.

Methodology:

Animal models: General and tissue specific AKo animal models are available in our laboratory. AKo/cTg; club cell specific CCSP-CRE/ATGL-flox; AT-2 cell specific SFTPC-CRE/ATGL-flox as well as LSL-KRAS intercrossed with ATGL-flox are some examples of our standard mouse lines that will be useful for future experiments.

Experimental models: Regenerative, immunological and inflammatory lung studies are performed in cooperation with the LBI-Lung Vascular Research, Graz, using naphthalene, HDM and LPS. Readouts include histological analyses, FACS and functional analyses such as, Flexi-Vent for lung function measurement. Genetic interaction of oncogenes and tumor suppressors are tested using the LSL-KRAS model that we acquired in an ongoing cooperation with Tyler Jacks, M.I.T., MA.

Metabolic studies: Metabolic cages are used at the animal facility of the IMBM, Graz. Special diets and metabolite tracing are also available. Lipidomics are performed at the Lipidomics Core Facility of the ZMF, Graz.

Molecular cloning, standard cancer cell culture and culture of primary cells are all well established.

References

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