Medical University of Graz

# Interplay of gluconeogenesis and glycolysis in lung cancer cells

## Summary

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| Supervisor: | Dr. Katharina Leithner |
| Availability: | This position is available. |
| Offered by: | Medical University of Graz |
| Application deadline: | Applications are accepted between August 18, 2021 00:00 and October 04, 2021 23:59 (Europe/Zurich) |

## Description

Background:

In rapidly growing cancers the extracellular fluid is often nutrient-poor despite the growth of new blood vessels. There is still a lack of understanding, how cancer cells adapt to these harsh conditions, especially to a lack of glucose. Recently, our group was the first to show that certain cancer cells can utilize the reverse pathway of glycolysis, gluconeogenesis, under glucose deprivation. We found that in lung cancer cells, the initial gluconeogenesis enzyme phosphoenolpyruvate carboxykinase (PEPCK, PCK2) is activated and enhances lung cancer cell survival under glucose starvation and promotes lung cancer growth [1,2]. PCK2 shows a broad expression in lung cancers, however PEPCK is absent from tumor cells in a subset of patients [3]. The PEPCK-derived metabolites have been found by us and others to be further be shunted towards 1) serine and glycine synthesis, 2) synthesis of glycerol-3-phosphate 3) oxidative and non-oxidative branches of the pentose phosphate pathway in cancer cells. However, the switch between gluconeogenesis and glycolysis, fueled by glucose or glycogen, is still poorly understood.

Hypothesis and Objectives:

The aim of this project is to explore the interplay of gluconeogenesis and glycolysis in lung cancer cells, its mode of regulation and the impact of nutrient and biosynthetic end product availability. Furthermore, the effects of dual gluconeogenesis and glycolysis inhibition on cancer cell metabolism, both, *in vitro* and *in vivo,* will be investigated.

Methodology:

The expression and activity of the gluconeogenesis enzyme PEPCK (PCK1 and PCK2), glycolysis enzymes and glycogen degrading enzymes will be assessed under various nutritional conditions in different lung cancer cell lines. We will knock-down PEPCK (PCK2 or the cytoplasmic isoform PCK1) by siRNA and stably expressed shRNA or utilize a pharmacological inhibitor of PEPCK. Similarly, we will inhibit glyco(geno)lysis by RNAi-mediated silencing or pharmacological approaches. We will study the flux through the gluconeogenesis/glycolysis pathway by stable isotopic ($^{13}$C) tracing and metabolite analysis by gas or liquid chromatography/mass spectrometry (by the group/the candidate and by our international collaborator) and/or nuclear magnetic resonance spectroscopy (by our collaborator at the Medical University of Graz). The experiments will be largely performed in lung cancer cell lines *in vitro* under different starvation conditions or *in vivo*, in mouse xenograft models. This approach will allow to determine the relative contribution of each metabolic pathway to central metabolism and end product formation (e.g. serine and glycine biosynthesis). Functional studies on cancer cells will determine the role of each metabolic pathway for proliferation, colony formation or cell survival. Moreover, we will infer reactive oxygen species (ROS) formation and redox balance using different methods and characterize the signaling pathways involved. The relevance of the findings for human tumors will be further addressed by utilizing *ex vivo* cultured explants of surgically removed human lung cancers. The results of the study will foster the understanding of cancer cell metabolism in nutrient-limited conditions, focusing on a poorly characterized metabolic pathway.

The Group:

Our group, consisting at present of the PI, two PhD students and a technician/diploma student, is located in the vicinity of the University hospital Graz in a research facility offering cutting edge technologies. We highly encourage motivated, curious students with interest in metabolism and cancer to apply for this position.

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References:

1. Leithner K, Hrzenjak A, Trotzmuller M, Moustafa T, Kofeler HC, Wohlkoenig C, Stacher E, Lindenmann J, Harris AL, Olschewski A, Olschewski H. PCK2 activation mediates an adaptive response to glucose depletion in lung cancer. Oncogene 2015, 34(8):1044-1050. doi: 10.1038/onc.2014.47

2. Leithner K, Triebl A, Trotzmuller M, Hinteregger B, Leko P, Wieser BI, Grasmann G, Bertsch AL, Züllig T, Stacher E, Valli A, Prassl R, Olschewski A, Harris AL, Köfeler HC, Olschewski H, Hrzenjak A. The glycerol backbone of phospholipids derives from noncarbohydrate precursors in starved lung cancer cells. Proc Natl Acad Sci U S A 2018, 115(24):6225-6230. doi: 10.1073/pnas.1719871115

3. Smolle E, Leko P, Stacher-Priehse E, Brcic L, El-Heliebi A, Hofmann L, Quehenberger F, Hrzenjak A, Popper HH, Olschewski H, Leithner K. Distribution and prognostic significance of gluconeogenesis and glycolysis in lung cancer. Mol Oncol. 2020, 14(11):2853-2867. doi: 10.1002/1878-0261.12780.