Medical University of Graz

Gluconeogenesis in tumor promoting stroma cells

Summary

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Supervisors:	Dr. Katharina Leithner Dr. Joerg Lindenmann
Availability:	This position is available.
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Description

Background: In tumor cells, an enhanced rate of glucose consumption promotes rapid growth and proliferation. High rates of glycolysis ensure that glycolytic intermediates are available to be shunted towards important biosynthetic pathways. Still, the tumor's high demand for nutrients like glucose is frequently not met by an adequate supply. Cancer cells, as well as accompanying non-neoplastic cells, constantly have to adapt to a low nutrient microenvironment. Recently, our group was the first to show that certain cancer cells can utilize the reverse pathway of glycolysis, gluconeogenesis, to generate crucial intermediates 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 and other cancer types, however PEPCK is absent from tumor cells in a subset of patients [3]. Macrophages and other stroma cells are recruited and re-programmed by tumor cells to promote angiogenesis and facilitate tumor cell migration. However, they also interact with tumor cells to support their metabolism.

Hypothesis and Objectives: Whether PEPCK is functionally expressed in tumor-associated macrophages or fibroblasts to promote (partial) gluconeogenesis and the local release of metabolites is not known. A high level of PCK2 expression was detected in lung macrophages including tumor macrophages in a recent study on human lung cancers [3]. PEPCK/PCK2 allows the synthesis of glycolytic intermediates from non-carbohydrate precursors. The PEPCK-derived intermediates may 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, thus providing ribose-5-phosphate and NADPH, or 4) glucose biosynthesis. As a hypothesis, macrophages or fibroblasts release products generated via PEPCK, including serine, glucose or phospholipids, to feed nearby nutrient-starved tumor cells, thus promoting their proliferation and survival.

Methodology:

The expression and activity of the gluconeogenesis enzyme PEPCK will be assessed in tumor-associated macrophages and fibroblasts, freshly isolated from human lung cancers and/or cultured under different nutritional conditions along with markers for pro-tumorigenic polarization of the macrophages. The tumors will be derived from surgery at the Division of Thoracic Surgery, Medical University of Graz. Moreover, macrophages will be differentiated from human blood-monocytes and primed to different phenotypes. We will silence PEPCK (PCK2 or the cytoplasmic isoform PCK1) by siRNA and/or utilize bone marrow-derived macrophages and fibroblasts from WT or PCK2 knockout mice. The role of gluconeogenic macrophages or fibroblasts on tumor cell survival, migration and 3D growth, will be assessed under glucose-deprived or glucose-replete conditions. Stable isotope labelling strategies and gas chromatography/mass spectrometry will be employed to determine the fate of gluconeogenic precursors, e.g. lactate and glutamine, in glucose-starved macrophages/fibroblasts and their utilization as tumor cell nutrients.

References:

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Medical University of Graz

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