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Gluconeogenesis is activated in macrophages under glucose starvation

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Background/Aims: Cancer cells have a rewired metabolism and enhanced glucose consumption promotes growth and proliferation. As tumor cells outgrow their supply, steep gradients for glucose emerge and both, cancer and non-neoplastic cells need to adapt to glucose starvation. The key gluconeogenesis enzyme, PEPCK (PCK1/2), was shown to support tumor cell survival under low glucose in some cancers. PCK2 allows synthesis of glycolytic intermediates from non-carbohydrate precursors that are shunted towards various pathways. However, gluconeogenesis may support tumor-associated macrophages, one of the main tumor-infiltrating immune cells, as well. Whether PEPCK is functionally expressed in macrophages to promote gluconeogenesis is not known. Recently, high PCK2 expression was found in lung macrophages including tumor-associated macrophages in a study on human lung cancers.

Method/Results: PCK2 expression analysis in IFN-?/LPS (M1) or IL-4 (M2) polarized monocyte-derived macrophages revealed consistent expression of PCK2 on mRNA and protein level, irrespective of glucose abundance. Assessing cell metabolism with stable isotopic labelling and GC-MS, we verified functional expression of PCK2. Using 13C5-glutamine as tracer, we detected labelling of TCA cycle metabolites and phosphoenolpyruvate and glycerol-3-phosphate, showing that glutamine fuels initial steps of gluconeogenesis, primarily under low glucose. Thus, we found a trend towards higher gluconeogenesis activity in macrophages upon glucose starvation.

Conclusion: Macrophages functionally express PCK2 and generate glycolytic/gluconeogenic intermediates directing gluconeogenesis under low glucose. The data suggest a metabolic switch in macrophages facing a low glucose environment, however further work is needed to assess the role of gluconeogenesis in different macrophage functions. This study sheds light on macrophage metabolism upon unstable nutritional conditions, as present in the tumor microenvironment.