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Glutamine drives glucose-independent TCA cycle

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Rationale: Cancer cells rely on their ability to reprogram their metabolic pathways to be able to survive and proliferate in the tumor microenvironment which is often hypoxic and nutrient-deprived. This study explored the alternate metabolism of cancers cells under aerobic, hypoxic and glucose-deprived conditions.

Methods: We used high-field NMR, in parallel with GC-MS, and direct infusion nanospray FT-ICR-MS as well as stable isotope-resolved metabolomics to trace the fate of ^{13}C and 15N from labeled glucose or glutamine in the P493 human B lymphoma under aerobic, hypoxic glucose-deprived conditions. Levels of specific enzymes, which are involved in glucose and glutamine metabolism, were determined by immunoblotting and LC-MRM-MS and compared with the metabolomic profiles.

Main Results: We discovered that glutamine metabolism, for bioenergetics and redox homeostasis, persisted for cell growth and survival under hypoxic conditions in which glucose was favorably converted to lactate. Most importantly, this study uncovered a glucose-independent glutamine-driven TCA cycle which is advantageous to cancer cells subjected to glucose deficiency and/or hypoxia in the tumor. Further in this pursuit, the anti-proliferative therapeutic effect of a drug-like molecule BPTES which inhibits glutaminase was observed in neoplastic cells in vitro and in a tumor xenograft model in vivo.

Conclusions: A sustained glutamine metabolism was discovered in this study, whereby cancer cells can oxidize glutamine through TCA cycle in hypoxia and glutamine metabolism alone can sustain TCA cycle for cell growth and survival in the absence of glucose. This allows cancer cells to proliferate and survive under the harsh hypoxic and nutrient-deprived conditions of the tumor microenvironment. These findings not only advance the understanding of cancer metabolism but also pave the way for novel therapeutic targets.

Biography

Dr. Anne Le obtained her basic science training from the Rene Descartes Paris V University, Cochin Port-Royal School of Medicine, in France and the Johns Hopkins University. She did her clinical training at Nancy University Hospital Center, in France. Her research is primarily focused on cancer metabolism. Her research was the first targeting lactate dehydrogenase A (LDHA), a critical enzyme of the Warburg effect in cancer, using a drug-like small molecule called FX11 (PNAS, 2010). FX11 has shown an anti-tumorigenic effect in mice models of human lymphoma and pancreatic cancer through the increased production of reactive oxygen species and cell death. Dr. Le recently applied metabolomics technologies to extensively study glycolysis and glutaminolysis. This work resulted in a breakthrough discovery of glucose-independent glutamine-driven TCA cycle (Cell Metabolism, 2012).

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