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Iliopoulos Laboratory

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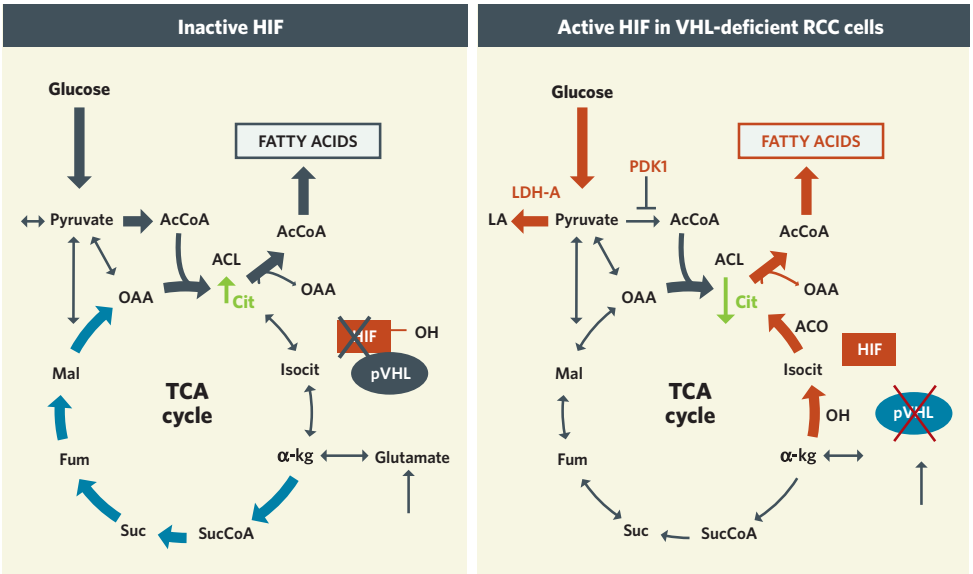
The Iliopoulos laboratory works on the main mechanisms underlying the reprogramming of cancer cell metabolism and cancer angiogenesis with the goal to develop mechanism-based strategies for selectively killing cancer cells. We use Renal Cell Carcinoma (RCC) as a model disease of altered cancer metabolism and angiogenesis mechanisms. Cancer cells transform their metabolism to adapt to the needs of fast growth and to compete with the surrounding normal cells for nutrients and oxygen. In addition to a reprogrammed metabolism, cancer cells stimulate the growth of new blood vessels that bring blood to them, a phenomenon known for many years as "cancer angiogenesis". The laboratory identifies and validates therapeutic targets that disrupt these processes.

Discovery and development of hypoxia inducible factor 2a (HIF2a) inhibitors for treatment of renal cell carcinoma and other HIF2a-dependent cancers

We screened libraries of chemical compounds and discovered chemical molecules that significantly and specifically decrease the expression of HIF2a (Zimmer M. et al. *Molecular Cell* 2008; 32(6): 838-48). We used these HIF2a inhibitors as chemical biology probes and discovered that they suppress the expression of HIF2a by activating IRP1. We thus proved a crosstalk between the iron and oxygen sensing mechanisms within the cell. We demonstrated that the HIF2a inhibitors discovered are "active" and that they reverse the consequences of VHL protein loss (Metelo AM. *Journal Clinical Investigation* 2015; 125(5): 1987-97). Our chemical HIF2a inhibitors are very promising agents for treating RCC.

Targeting the metabolic reprogramming of RCC and HIF2a expressing tumors; from the lab to the bedside

We used metabolic flux analysis to show that hypoxic cells use glutamine as a carbon source for anabolism. We showed that low oxygen levels or HIF2a expression reprogrammed cells to use glutamine in a "reverse" TCA cycle to produce the metabolites required for anabolic reactions, a process called Reductive Carboxylation. These observations provided insights into a mechanism by which hypoxic and HIF2a expressing cancer cells compensate for the Warburg phenomenon (Metallo et al. *Nature* 2012; 481(7381): 380- 4). We delineated the mechanism driving Reductive Carboxylation and proved that reductive carboxylation does not only happen in cultured cells, but can also be detected in human RCC tumors growing as xenografts in mice. We therefore provided for the first time, in vivo evidence for the utilization of glutamine in tumors through reductive carboxylation (Gameiro et al. *Cell Metabolism* 2013; 17(3): 372-385). Recently, we showed that inhibition of Glutaminase 1 (GLS1) decreases significantly the intracellular pyrimidines and results in DNA replication stress in HIF-hypoxia driven cancer cells. Treatment of cancer cells with GLS1 and PARP inhibitors resulted in dramatic suppression of RCC in xenograft models (*J Clin Invest.* 2017; 127(5): 1631-1645).



Expression of Hypoxia Inducible Factor HIF2a rewires the central carbon metabolism in renal cell cancer.

We brought these fundamental observationsof our laboratory on glutamine metabolism to the clinic, testing the combination of GLS1 inhibitors with PARP inhibitors in renal cancer, clear cell ovarian and prostate cancer

Clinical and translational studies to identify resistance to the HIF2a inhibitor Belzutifan.

Belzutifan has been approved by FDA for treatment of VHL disease related RCC, hemagioblastoma and pancreatic neuroendocrine tumors. Our laboratory and the MGH VHL and Hemangioblastoma Centers are leading clinical trials for the optimal use of this first in class oral medication. In addition, we use patient tissue, in vitro and in vivo models to discover mechanisms of resistance to this medication.

Selected Publications:

Okazaki A, Gameiro PA, Christodoulou D, Laviollette L, Schneider M, Chaves F, Stemmer-Rachamimov A, Yazinski SA, Lee R, Stephanopoulos G, Zou L, **Iliopoulos O**. Glutaminase and poly(ADP-ribose) polymerase inhibitors suppress pyrimidine synthesis and VHL-deficient renal cancers. *J Clin Invest.* 2017; 127(5): 1631-1645. Targeting metabolism in RCC. *Nature Reviews Nephrology*. 2017; 13, 320.

Laviolette LA, Mermoud J, Calvo IA, Olson N, Boukhali M, Steinlein OK, Roider E, Sattler EC, Huang D, Teh BT, Motamedi M, Haas W, **Iliopoulos O**. Negative regulation of EGFR signalling by the human folliculin tumour suppressor protein. ***Nat Commun***. 2017; 28;8: 15866.

Metelo AM, Noonan HR, Li X, Jin YN, Baker R, Kamentsky L, Zhang Y, van Rooijen E, Shin J, Carpenter AE, Yeh JR, Peterson RT, **Iliopoulos O.** Treatment of VHL disease pheno-types with small molecule HIF2a inhibitors. *Journal Clinical Investigation*. 2015; 125 (5):1987-97.

Gameiro PA, Yang J, Metelo AM, Pérez-Carro R, Baker R, Wang Z, Arreola A, Rathmell WK, Olumi A, López-Larrubia P, Stephanopoulos G and **Iliopoulos O**. HIF mediated reductive carboxylation occurs in vivo through regulation of citrate levels and sensitizes VHL-deficient cells to glutamine deprivation. *Cell Metabolism.* 2013; 17 (3): 372-385.

Metallo CM, Gameiro PA, Bell EL, Mattaini KR, Yang J, Hiller K, Jewell CM, Zachary R. Johnson JR, Irvine DJ, Guarente G, Kelleher JK, Vander Heiden MG, **Iliopoulos O***, Stephanopoulos G*. Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. *Nature*. 2011; 481 (7381): 380-4, Nov 20.

Zimmer M, Ebert BL, Neil C, Brenner K, Papaioannou I, Melas A, Tolliday N, Lamb J, Pantopoulos K, Golub T, **Iliopoulos O**. Small-molecule inhibitors of HIF-2a translation link its 5'UTR iron-responsive element to oxygen sensing. ***Molecular Cell***. 2008; 32(6): 838-48.

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