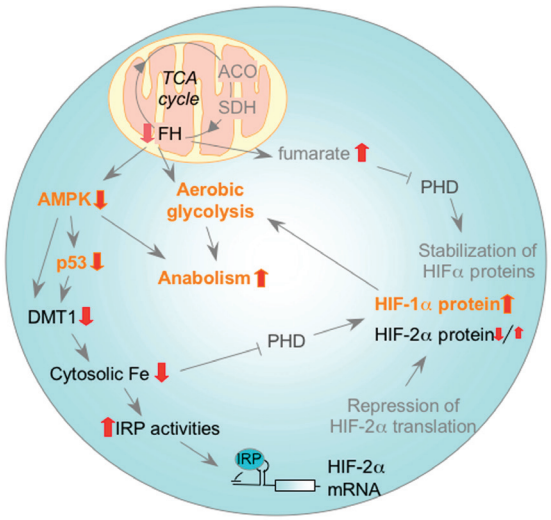
Collaborating to

Outwit HLRCC's Pathways

Marston Linehan, M.D., Chief of CCR's Urologic Oncology Branch, has spent his entire career at CCR crafting better approaches to treating kidney cancer, and he has done so by establishing effective collaborations and collecting properly annotated tissue samples. Almost 30 years ago, when he partnered with Berton Zbar, M.D., then Chief of the Laboratory of Immunobiology, to identify the first mutation that established a genetic basis for kidney cancer, he had no way of knowing the amount of genetic diversity he was facing. What Linehan did recognize was the importance of stored tissue and samples from kidney cancer families. This foresight, along with his ability to establish strategic collaborations, has enabled Linehan and his colleagues to identify and study more underlying mutations, not just in clear cell renal cell carcinoma, but also in papillary kidney cancer, TFE3 kidney cancer, hereditary chromophobe kidney cancer, and most recently in hereditary leiomyomatosis renal cell carcinoma (HLRCC).



In this working model of cells deficient in the fumarate hydratase (FH) gene, impairment of the Kreb's cycle results in a shift of energy production from respiration to glycolysis that induces an AMP-activated protein kinase dependent decrease in p53 and increased expression of hypoxia inducible factor-1.

(*Figure: Marston Linehan, CCR*)

When studying HLRCC, Linehan and his research team collaborated with Tracey Rouault, M.D., of the Eunice Kennedy Shriver National Institute of Child Health and Human Development, to determine how kidney cells missing the fumarate hydratase (FH) gene—an essential enzyme of the Krebs citric acid cycle—manage to survive and thrive. Knowing HLRCC patients lacked the FH gene, Linehan once again turned to his collection of kidney cancer tissue samples. Linehan worked with Rouault to demonstrate that inactivation of the Krebs cycle in FH-negative cells and tissues from HLRCC patients results in a glycolytic shift that decreases levels of AMP-activated protein kinase (AMPK). The team showed that when AMPK signaling is reduced, the expression of tumor suppressor gene p53 also is reduced, and hypoxia inducible factor is increased.

Linehan and his collaborators wanted to know how HLRCC cells manage to supply themselves with energy under such restricted conditions, so again they established an appropriate collaboration. This time they turned to colleagues Ralph DeBerardinis, M.D., Ph.D., at The University of Texas Southwestern Medical Center, and Navdeep Chandel, Ph.D., at Northwestern University, for their expertise in techniques such as C13 glucose and glutamine metabolite tracking. Working together, they demonstrated that these tumor cells have defective mitochondria that use a glutamine-dependent reductive carboxylation pathway rather than the typical oxidative path to compensate for the metabolic shift in these rapidly growing fumarate-hydratase-deficient kidney cancer cells.

This work, and subsequent, in-depth radiolabeled tracer metabolite analysis performed with colleagues Teresa Fan, Ph.D., and Andrew Lane, Ph.D., at the University of Louisville, is revealing some potential targets and novel approaches to therapy for HLRCC and related malignancies.

"These results are very encouraging; these tumor cells are completely dependent on this alternate energy pathway for rapid growth," says Linehan. "So, hypothetically, we can block any of the pathway components to stop HLRCC cells' growth."

To learn more about Dr. Linehan's research, please visit his CCR Web site at http://ccr.cancer.gov/staff/staff.asp?Name=linehan.