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Therapeutic Targeting of FLCN-Deficient Renal Cancers

Principal Investigator: ILIOPOULOS, OTHON
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PUBLIC ABSTRACT

Drs. Birt, Hogg, and Dube' were three physicians who first described the occurrence of multiple and recurrent kidney (renal) cancers in several members of the same family. The affected family members also developed benign and characteristic skin "bumps" that are known as fibrofolliculomas and often developed a "collapsed lung," a condition called pneumothorax. The genetics of these families indicated that there is a gene connected to the disease, termed Birt-Hogg-Dube' (BHD) disease. This gene was identified and called Folliculin (FLCN) in 2006 by Drs. Marston Linehan and Laura Schmidt at the National Institutes of Health.

Tumor DNA sequencing and genetic material from the patients with the disease indicated that this is a tumor suppressor gene, the absence of which causes renal cell carcinoma (RCC). As with other tumor suppressor genes, understanding how the protein product of the gene prevents tumor development opens new doors in understanding how cancer cells develop. Such insights are required for the rational design of effective drugs and strategies to treat established renal cancer or to design methods to prevent renal cancer development.

One fascinating detail is that the renal cancers in BHD patients may be of almost any known histology or often they are termed "not classified" because they have simultaneous histologic features of clear cell, papillary, chromophobe, and oncocytoma, often a hybrid between these histologic types. It therefore appears that FLCN is linked to these "rare forms of RCC." Our proposal addresses two mandates of CDMRP interest; it investigates targeted therapy in rare forms of kidney cancer.

Since the identification of FLCN as the cause of inherited or sporadic forms of rare RCC, the Sabatini laboratory showed that FLCN works as a "facilitator" of molecular "switch" proteins called GTPases, specifically by acting as a GTPase Activating Protein (GAP). The GAP activity by FLCN stimulates the activation of a kinase called mTORC1, which is a key protein for cancer cell proliferation and tumor growth. This astute biochemical insight left us with a paradox: Why would FLCN, a tumor suppressor, stimulate a kinase whose activity is associated with development of cancer?

We addressed this paradox head on by looking for other targets of the GAP activity of FLCN. In our recent publication in Nature Communications, we showed that FLCN acts as a GAP and activates the protein Rab7A. Rab7A in turn accelerates the internalization and inactivation of EGFR, a kinase on the surface of cancer cells that has been very closely associated with cancer development. By downregulating the function of EGFR, FLCN thereby suppresses tumor formation. This is an innovative approach that sets the field in a new direction.

Our proposal is based on the following key observations:

(1) EGFR is not the only cell surface kinase that is suppressed by FLCN. We show that another cancer-related kinase, c-Met, is also suppressed. We have reason to believe that FLCN regulates a whole panel of cell surface kinases in a way similar to EGFR, because the "internalization" of these kinases is a general mechanism of regulation.

(2) We showed that FLCN suppresses protein translation and it binds to two translation-promoting factors that are GTPases. We therefore propose to take a system biology approach in order to profile all the kinases that are regulated by FLCN and to evaluate which kinases can be used to target FLCN-driven, rare RCCs. We also propose a series of experiments that will uncover the biochemical details of how FLCN suppresses protein translation.

(3) The third goal is to use mutants of FLCN to find out if all these functions depend on different parts of the protein and can be separated from each other. Such a "distribution" of functions (called "domains") will help us understand which of these functions are important for tumor suppression.

Chromophobe, oncocytoma, and rare clear cell/papillary hybrids are all FLCN-driven, rare tumors that develop in Service members, their families, Veterans, and the American public. Our experiments will advance our understanding of how renal cells become cancerous when they lose FLCN and will enable us to treat and/or prevent these forms of renal cancer.

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