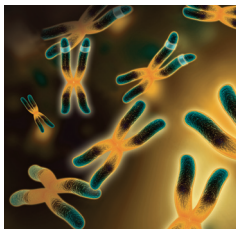
HIF1α Is a Kidney Cancer Suppressor Gene

- The *HIF1α* locus located on chromosome 14q is often deleted in kidney cancer.
- Somatic *HIF1α* mutations identified in kidney cancer are loss of function.
- Downregulation of wild-type HIF1α promotes growth of renal carcinoma *in vivo*.



Clear cell renal carcinoma (CCRC) is the most common type of kidney cancer, often caused by homozygous loss of function of the von Hippel–Lindau *VHL* tumor suppressor gene. One important function of the *VHL* gene product, pVHL, is to target the alpha subunit of the hypoxia-inducible factor (HIF) transcription factor for proteasomal degradation. Deregulation of HIF target genes is often found in kidney cancers, and HIF2α is known to be a kidney cancer oncoprotein. Chromosome 14q, which contains *HIF1α*, is also commonly lost in CCRC. These observations led Shen and colleagues to investigate whether *HIF1α* functions as a tumor suppressor gene in CCRC. Genetic analysis of multiple tumor types and multiple CCRC cell lines confirmed the frequency of focal homozygous deletions of the *HIF1α* locus on chromosome 14q in kidney cancer. In *HIF1α*-negative kidney cancer cells, re-expression of wild-type HIF1α suppressed cell proliferation. However, re-expression of *HIF1α* genomic deletion variants as well as known somatic *HIF1α* mutations failed to suppress renal carcinoma growth. The reciprocal experiment, in which wild-type HIF1α was downregulated in HIF1α-positive cancer cells, showed enhanced proliferation of tumor cells both *in vitro* and *in vivo*. Together, the genomic and functional studies identify *HIF1α* as a tumor suppressor gene in CCRC, a finding that provides important insight into the functional balance of HIF1α and HIF2α and explains the frequent loss of chromosome 14q in this disease. ■

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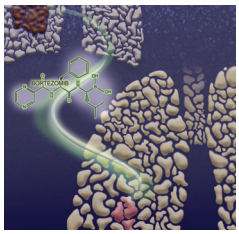
NF-κB Is a Promising Therapeutic Target in Lung Adenocarcinoma

- NF-κB inhibitor treatment reduced tumor volume and increased survival in mouse models of lung cancer.
- Activation of the NF-κB pathway predicts sensitivity to small molecule NF-κB inhibitors.
- Prolonged NF-κB inhibition leads to acquired resistance of lung tumors in mice.



Lung cancer remains the leading cause of cancer death worldwide. Recent studies have associated aberrant signaling through the NF-κB pathway with the development of a number of cancers, including lung cancer. Using a genetically engineered mouse model of human lung adenocarcinoma, in which tumors showed activation of the NF-κB pathway, Xue and colleagues investigated whether NF-κB may be a novel therapeutic target. In its inactive state, NF-κB is sequestered in the cytoplasm by its inhibitor, IκB. Upon pathway activation, IκB is targeted for degradation by the proteasome, allowing NF-κB to translocate to the nucleus and bind DNA. Bortezomib, a proteasome inhibitor, has been shown to target the NF-κB pathway. Importantly, treatment of the mutant mice with bortezomib resulted in inhibition of NF-κB signaling, apoptosis of tumor cells, and tumor regression. Similar results were achieved with the slightly more selective small molecule inhibitor Bay-117082, which inhibits phosphorylation of IκB, thereby confirming the therapeutic efficacy of inhibition in these tumors. Treatment with bortezomib or Bay-117082 also prolonged survival. In both cases, however, tumors ultimately developed resistance to treatment, but in the absence of reactivation of NF-κB activity, suggesting a mechanism of acquired resistance independent of NF-κB. Taken together, the results demonstrate the therapeutic efficacy of NF-κB inhibition in tumors with activation of the NF-κB pathway, and suggest that combination therapy may be necessary to overcome acquired resistance in lung and potentially other cancers characterized by activation of NF-κB. ■

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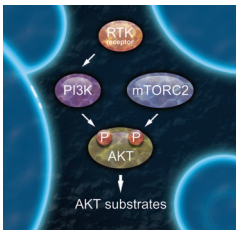
Biphasic Regulation of AKT Signaling

- Dual mTORC1 and mTORC2 inhibitor has biphasic effect on AKT signaling.
- AKT is reactivated through relief of RTK feedback inhibition.
- Combined inhibition of mTOR and RTKs abolishes AKT signaling.

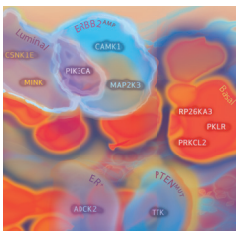


Activation of phosphoinositide 3-kinase (PI3K) signaling is found in a variety of cancers and the mTOR protein kinase is an important component of this pathway. mTOR exists in two complexes, mTORC1 and mTORC2. Rodrik-Outmezguine and colleagues show that the ATP-competitive mTOR kinase inhibitor AZD8055, which inhibits both mTORC1 and mTORC2 activities, has a biphasic effect on AKT. First, inhibition of mTORC2 leads to AKT serine 473 (S473) dephosphorylation and rapid, transient inhibition of AKT T308 phosphorylation and AKT signaling. Second, through its inhibition of mTOR kinase activity, AZD8055 also led to activation of receptor tyrosine kinase (RTK) signaling, activation of PI3K signaling and, despite persistent inhibition of mTORC2 activity and AKT S473 phosphorylation, reactivation of AKT activity. Combined inhibition of mTOR with the HER2 inhibitor lapatinib caused cell death and tumor regression *in vivo*, highlighting the clinical potential of combining mTOR inhibitors with other signal transduction inhibitors. ■

See article, p. 248.

Functional Viability Profiles of Breast Cancer

- High-throughput strategy included more than 700 siRNAs targeting kinases in 30 models of breast cancer.
- Functional screen is based on synthetic lethality.
- Identified growth-critical genes and potential therapeutic targets in breast cancer.



The goal of targeted therapies is to block molecules required by tumor cells, but not normal cells, thus minimizing negative side-effects. Lord, Ashworth, and colleagues used a high-throughput RNA interference (RNAi) functional genetic screen that takes advantage of synthetic lethality to identify genes critical for tumor cell survival. Synthetic lethality occurs when a combination of mutations in two or more genes leads to cell death, whereas a mutation in only one of these genes does not. Functional screening using siRNAs targeting 714 known and putative protein kinase genes was used to screen more than 30 breast cancer cell lines and then combined with gene expression, gene mutation, and genomic analyses. The authors sought to identify genes that caused significant lethality in some, but not all, cell lines reasoning that these genes have critical functions in tumor, but not normal, cells. Because kinases have been shown to be druggable genes, the genes identified in the screen are thus candidate therapeutic targets. This large-scale functional profiling strategy enabled classification of breast cancers into subgroups distinct from established subtypes and identified potential new therapeutic targets for *PTEN*-mutated and estrogen-receptor–positive breast cancers. ■

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Note: *In This Issue* is written by *Cancer Discovery* Editors. Readers are encouraged to consult the articles referred to in each item for full details on the findings described.

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