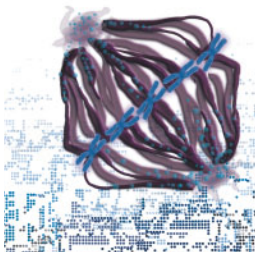
Integrative Analysis Provides Insight into Prostate Cancer Progression

- The gene expression profiles of NEPC and PCA differ significantly.
- *AURKA* and *MYCN* are concurrently amplified in 40% of NEPC.
- Aurora kinase inhibitors may be effective in NEPC.



Neuroendocrine prostate cancer (NEPC) is an aggressive subtype of prostate cancer that evolves from prostate adenocarcinoma (PCA). Most patients who develop NEPC survive less than 1 year, and there is currently no standard treatment because so little is known about its molecular characteristics. Beltran and colleagues therefore utilized next-generation RNA sequencing and oligonucleotide arrays in order to better understand the distinguishing molecular features of NEPCs and PCAs and identify potential avenues for targeted therapy in NEPC. Integration of the expression and copy number data showed that *Aurora kinase A* (*AURKA*) was significantly overexpressed and amplified in NEPC compared with PCA. Because AURKA had previously been shown to interact with the MYCN (N-myc) oncogene in neuroblastoma, another aggressive neuroendocrine tumor, the authors analyzed *MYCN* expression and likewise discovered significant upregulation in NEPC compared with PCA. *AURKA* and *MYCN* were amplified in 40% of NEPCs analyzed compared with only 4% of PCAs. Strikingly, amplification of these two genes was concurrent in more than 90% of AURKA- and MYCN-positive NEPCs, suggesting that these two oncogenes cooperate in the progression of PCA to NEPC. Indeed, MYCN interacts with and stabilizes AURKA, and both MYCN and AURKA induce expression of neuroendocrine markers in prostate cells. Pharmacologic inhibition of AURKA preferentially decreased tumor size in NEPC xenograft models compared to PCA and suppressed neuroendocrine marker expression, suggesting that Aurora kinase inhibitors should be considered for NEPC therapy. ■

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Cell-Specific Effects Mediate Drug Toxicity and Therapeutic Response

- Tumor-specific inhibition of NF-κB sensitizes melanoma cells to doxorubicin.
- IKKβ loss in host cells causes treatment-induced toxicity due to an inflammatory response.
- NF-κB blocking agents may be most effective when targeted to specific cell types.

The NF-κB pathway plays critical roles in immunity and inflammation as well as cancer progression and chemoresistance. Enzler and colleagues studied the feasibility of targeting the NF-κB pathway with a small-molecule inhibitor of IκB kinase (IKK) in melanoma, a highly chemorefractory cancer. Strikingly, combined treatment with the IKK inhibitor and doxorubicin induced almost complete tumor regression in melanoma xenografts; however, the animals suffered severe side effects. The authors observed neutrophilic invasion of the tumor site independent of tumor regression, leading them to hypothesize that inhibition of NF-κB signaling in distinct cell types underlies toxicity and chemosensitization. To prove this, they selectively inhibited NF-κB signaling in tumor cells by stably expressing an NF-κB inhibitor in melanoma cells or in host myeloid cells by conditional inactivation of IKKβ. Doxorubicin prevented tumor growth without neutrophilic invasion or severe side effects when tumor-intrinsic NF-κB signaling was inhibited. However, doxorubicin treatment had no effect on tumor growth in IKKβ-deficient mice, and instead led to death associated with necrosis and neutrophilic invasion of the tumor tissue. The authors further demonstrate that the pathologic effects of NF-κB inhibition in host myeloid cells are due to increased production of the inflammatory cytokine interleukin-1β. These findings suggest that although useful for sensitizing tumors to cytotoxic agents, NF-κB blocking agents may cause toxicity if not specifically targeted to tumor cells. ■

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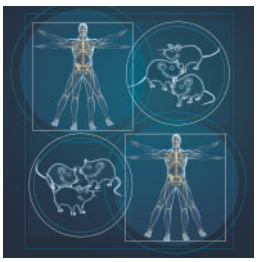
"Xenopatients" Implicate *HER2* Amplification in Cetuximab Resistance

- Patient-derived xenograft cohorts can be used for preclinical population-based studies.
- *HER2* amplification is observed in 36% of cetuximab-resistant metastatic colorectal cancer.
- Targeting both HER2 and EGFR in metastatic colorectal cancer may improve clinical outcome.



Cancer cell lines and genetic mouse models that are currently used for preclinical compound testing are not always predictive of clinical outcome because they inherently fail to recapitulate tumor heterogeneity. Bertotti and colleagues developed a platform to circumvent these limitations by directly implanting and serially transplanting surgical material from a panel of 130 human metastatic colorectal cancer tumors into mice to create "xenopatients." The authors utilized their large xenopatient cohort to identify novel biomarkers of resistance to cetuximab, an anti–epidermal growth factor receptor (EGFR) monoclonal antibody that has been approved for treatment of metastatic colorectal cancer but only elicits a clinical response in 10% of patients. Importantly, they found that xenopatient tumors both morphologically and genomically resemble the original patient tumors, exhibit individual heterogeneity, and recapitulate the cetuximab response rate observed in clinical trials. Genome-wide expression profiling of xenopatients revealed that *HER2* amplification was observed in 36% of tumors lacking mutations in *KRAS*, *NRAS*, *BRAF*, or *PIK3CA* ("quadruple-negative" tumors), all of which were resistant to cetuximab. The authors then performed a proof-of-principle randomized "xenotrial" to determine whether HER2 is a valid therapeutic target in cetuximab-resistant tumors. Combination treatment with pertuzumab, an antibody that disrupts HER2–EGFR dimerization, and lapatinib, a small-molecule inhibitor with high affinity for both HER2 and EGFR, significantly inhibited tumor growth in HER2-positive, quadruple-negative xenopatients, suggesting this population-based xenopatient approach can be used to study drug response and stratify patients in a preclinical setting. ■

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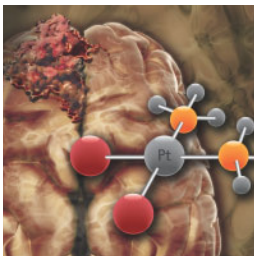
mTORC2–NF-κB Signaling Underlies Glioblastoma Drug Resistance

- Elevated mTORC2 signaling is present in nearly 60% of GBM.
- mTORC2 is a potent activator of NF-κB and a mediator of chemoresistance.
- Dual inhibition of mTORC1 and mTORC2 may be an effective GBM therapy.



Although the phosphoinositide-3 kinase (PI3K) pathway is hyperactivated in nearly 90% of glioblastoma multiforme (GBM), pharmacologic inhibition of mTOR signaling with rapamycin has not been successful. mTOR exists in two distinct complexes—mTORC1 and mTORC2—consisting of mTOR, Raptor or Rictor, and other regulatory proteins. The role of mTORC2, if any, in GBM pathogenesis has been unclear. Tanaka and colleagues demonstrate that mTORC2 is activated following PTEN loss or EGFR activation, two of the most common genetic events in GBM. The authors also demonstrate that, unlike mTORC1, which is bound and inhibited by rapamycin, mTORC2 signaling is upregulated following rapamycin treatment, and is required for proliferation of GBM cell lines. Surprisingly, mTORC2 can activate NF-κB signaling in an Akt-independent manner to mediate chemoresistance. Inhibition of mTORC2 and NF-κB sensitizes resistant GBM xenografts to cisplatin treatment and results in an 80% decrease in tumor mass. Analysis of normal brain and tumor tissue from a large panel of patients with GBM showed that the majority of tumors exhibited coordinately elevated mTORC2 and NF-κB signaling, further implicating mTORC2 as a potential drug target in GBM. These findings establish a novel role for mTORC2 in NF-κB regulation and suggest that mTOR kinase inhibitors that block the signaling activities of both mTOR complexes will lead to improved clinical outcomes in GBM. ■

See article, p. 524.

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Cancer Discovery 2011;1:457.