lated tumorgraft model reveals activity of dovitinib against renal cell carcinoma, "Beyond the Abstract," nes Brugarolas, MD, PhD

Published on 03-18-2013

BERKELEY, CA (UroToday.com) - Our article establishes a proof-of-concept for a renal cell carcinoma (RCC) preclinical model. We show that tumor samples obtained from patients undergoing nephrectomy, when implanted orthotopically in mice, reproduce the characteristics and treatment responsiveness of RCC in patients. In the associated abstract, we report the experience of 94 cases. Tumor samples (8 mm^3) were implanted in the kidneys of mice without additives or disaggregation. Tumor cells could be detected in 37% of transplanted mice, but only 17% of the tumors could be stably passaged in mice. The tumors that grew in the mice (tumorgrafts) reproduced the features of the patient tumors at multiple levels. They preserved the histology. In addition, tumorgrafts preserved also the gene-expression pattern of the corresponding patient tumors. Furthermore, in the majority of cases, tumorgrafts more closely resembled the corresponding patient tumors than tumors from different patients resembled each other. These results indicate that tumorgrafts uniquely preserve the identity of the patient's tumor. Similar results were observed when deletion and insertion analyses were performed. Once again, tumorgrafts resembled the corresponding patient tumors to a larger extent than tumors from different patients. In addition, we found that over 90% of the mutations observed in patient tumors were present in the tumorgrafts. Furthermore, as best as we can determine, tumorgrafts passaged in the kidneys of mice do not accumulate new mutations. Thus, tumorgrafts reproduce the histology, gene expression, DNA copy number alterations, and mutations of patient tumors.

Interestingly, not only were features intrinsic to the tumor preserved in the tumors in mice, but also tumor effects in the host (paraneoplastic syndromes). More specifically, we found that tumorgrafts retained the ability to induce paraneoplastic hypercalcemia in mice. To determine whether this model may be used for drug development, we asked whether clear-cell RCC tumorgrafts in mice responded to drug therapy similarly to patients. For these experiments, 122 tumorgraft-bearing mice (from 8 different patient-derived lines) were treated with the following drugs: sunitinib, sirolimus (which is the dominant metabolite of temsirolimus and accounts for >75% of the drug circulating in patients after temsirolimus administration) and, as a control, erlotinib. Drug administration was adjusted using pharmacokinetic data in mice so as to reproduce exposures in humans. By comparison to control mice (treated with drug vehicle), both sunitinib and sirolimus inhibited tumor growth ($p < 0.0001$ for both). In contrast, erlotinib, which is believed to be inactive against clear cell RCC in humans, had no effect. These data show that tumorgrafts not only reproduce the molecular, cellular, and histological characteristics of RCC in humans, but also the treatment responsiveness.

Finally, we evaluated a drug in development, dovitinib. Dovitinib, like sunitinib, is an inhibitor of angiogenesis and blocks VEGFR2. However, in addition, dovitinib also blocks FGFRs, which are implicated in conferring resistance to inhibitors of angiogenesis. Interestingly, dovitinib was a more potent inhibitor of RCC growth than sirolimus or sunitinib in our tumorgraft model.

I speculate that the incorporation of tumorgraft models in the evaluation of novel targeted therapies could markedly improve oncology drug development. Presently, it is estimated that fewer than 25% of anticancer drugs tested in patients in clinical trials eventually receive approval by the FDA. This dismal success rate may be substantially improved through the incorporation of tumor models that reproduce the biology and treatment responsiveness of tumors in patients. In addition, these models may be used for pharmacodynamic studies to ascertain whether experimental agents are appropriately affecting their targets and to deepen our understanding of the biology of renal cancer.

Written by:

James Brugarolas, MD, PhD as part of *Beyond the Abstract* on UroToday.com. This initiative offers a method of publishing for the professional urology community. Authors are given an opportunity to expand on the circumstances, limitations etc... of their research by referencing the published abstract.

Department of Developmental Biology
Department of Internal Medicine Oncology Division
Simmons Comprehensive Cancer Center
University of Texas Southwestern Medical Center
Dallas, TX USA

A validated tumorgraft model reveals activity of dovitinib against renal cell carcinoma - *Abstract*

Share

TODAY®

nformation about *Beyond the Abstract*

nd the Abstract **dovitinib** **sirolimus** **sunitinib** **temsirolimus** **tumorgraft**

Comments (0) **Search**

Only registered users can write comments!

Topics on Urology Health, Urinary Leakage, Treating Prostate Cancer, Prostate Cancer Diagnosis, Urology News, Symptoms For Bladder Infection In Men

website design firm : **Web-JIVE LLC**