News

Biomarker test developed for rare form of renal cancer

A unique molecular fingerprint has been used by researchers at the University of Oxford, UK, to reliably identify a rare form of cancer know as hereditary leiomyomatosis and renal cell cancer.

The study documenting the development of the simple cheap and reliable test for the rare cancer biomarker has recently been published in *The Journal of Pathology*.

"Cancer can be caused by many different risk factors, but if we can pinpoint rapidly and accurately the particular type of tumor, we can provide more accurate advice to patients and their families, and perhaps diagnose cases at earlier, more treatable, stages," elaborated Patrick Pollard, a Beit Memorial Fellow at the University of Oxford.

"For the first time, we are now able to screen for tumors caused by this rare, but often very serious, condition using a test which is simple, cheap and reliable."

Hereditary leiomyomatosis and renal cell cancer is a rare disease that most often affects people aged 20–30 years. It first causes the development of benign but often painful tumors in the skin and the uterus. Between one in six and one in ten patients go on to develop an aggressive form of kidney cancer – papillary renal cell cancer.

The disorder is caused by an excess of a substance called fumarate, this leads to the development of cancer cells. Fumarate production is normally kept in check by an enzyme known as fumarate hydrase. Hereditary leiomyomatosis and renal cell cancer patients have a faulty gene responsible for the production of fumarate hydrase. The mutation in this gene is the unique marker that can now be screened for in under 2 h.

The new test can be used to screen cases of papillary renal cell cancer and in doing so identify undiagnosed cases of hereditary leiomyomatosis and renal cell cancer for genetic testing. The study's authors believe this test should be applied to papillary renal cell cancer patients to identify fumarate hydrase mutations and therefore allow advice to be provided to their families who may also risk developing the disorder and associated aggressive kidney cancer.

In the future "we hope that we will be able to detect succinated proteins in the blood/urine and therefore be able to

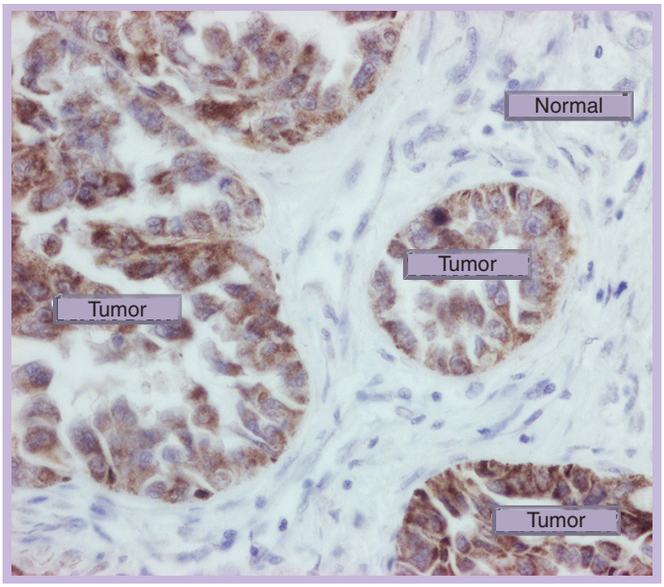

Figure shows that the 2SC stain (brown) is specific only to the tumor and not the surrounding nontumor (or normal) tissue.

Image courtesy of Patrick Pollard, University of Oxford, UK

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provide a noninvasive diagnostic test", explained Pollard. "At present we can only screen pathology samples already removed from patients as some of these were undiagnosed it prompts testing and screening of family members."

"The approach is much more cost-effective than genetic testing of all possible cases using DNA sequencing. Tests like this can also help to identify other patients with the same mutation, paving the way for the development of targeted treatments for specific groups of patients. This approach is called stratified medicine and many scientists now believe it could revolutionize cancer treatment in the future," Pollard told *Therapy*.

Source: Bardella C, El-Bahrawy M, Frizzell N et al. *Aberrant succination of proteins in fumarate hydratase-deficient mice and HLRCC patients is a robust biomarker of mutation status.* J. Pathol. *DOI: 10.1002/path.2932 (2011) (Epub ahead of print).*

High blood pressure may act as sunitinib efficacy biomarker in metastatic renal cell carcinoma patients

Results from a study published in the *Journal of the National Cancer Institute* suggest that high blood pressure may be an indicator of improved outcome for patients with metastatic renal cell carcinoma.

The VEGF pathway inhibitor, sunitinib, which is approved for the treatment of advanced renal cell carcinoma, is commonly associated with hypertension. In the past, this resulting hypertension has been generally considered to be a side effect of therapy; however, recent findings suggest that this hypertension could also be viewed as a marker of sunitinib's efficacy.

In order to evaluate this association, Brian Rini, Associate Professor of Medicine at the Cleveland Clinic Taussig Cancer Institute, OH, USA, and his team performed a retrospective analysis of prospectively collected data. The study used data from four clinical trials involving patients with metastatic renal cell carcinoma who were treated with sunitinib, from which efficacy data from 544 patients were reviewed. Analysis of the maximum systolic and diastolic blood pressure data from these patients found that patients with metastatic renal cell carcinoma and sunitinib-induced hypertension had better clinical outcomes than patients without treatment-induced hypertension.

These findings suggest that by monitoring blood pressure, physicians may be able to use the resulting hypertension as a biomarker of the drug's efficacy, with high blood pressure indicating improved patient outcome for patients with metastatic renal cell carcinoma.

Several other potential biomarkers, including functional imaging and other treatment-related adverse events, have been considered, but their relative associations with patient outcome have not been as consistent compared with that of hypertension. However, before hypertension can be fully considered as a biomarker of cancer treatment efficacy, prospective trials and validation of the data set would need to be completed.

In an interview published in *Clinical Advances in Hematology & Oncology*, when asked about the viability of hypertension as a predictive biomarker for clinical outcome, Rini comments, "Not only our study data, but also other retrospective data … have seen that hypertension appears to correlate with outcome, accounting for time on therapy and other statistical analyses that have been applied. So, the idea seems very promising."

Sources: Rini BI, Cohen DP, Lu DR et al. *Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib.* J. Natl Cancer Inst. *103(9), 763–773 (2011); Rini B. Biomarkers: hypertension following anti-angiogenesis therapy.* Clin. Adv. Hematol. Oncol. *8(6), 415–416 (2010).*

Advanced kidney cancer risk increased by heavy smoking, study suggests

Researchers from Duke University Medical Center, Durham, NC, USA, looked at the association between smoking habits and kidney cancer. They found that patients who had smoked for a long period of time or who had smoked a high number of cigarettes were most likely to develop advanced renal cell carcinoma.

A total of 845 patients who had surgery for kidney cancer or renal cell carcinoma between 2000 and 2009 were considered in the study. Current and former smokers were found to be 1.5- to 1.6-times more likely to have advanced cancer than nonsmokers. The findings were presented at the American Urological Association's annual meeting, in Washington, DC, USA, in May.

The study also suggests that those who quit smoking reduce the risk of advanced kidney disease by 9% for every 10 years following smoking cessation.

In the press release, news conference moderator Toby Kohler said, "For kidney cancer, it is true that kidney tumors are more often being detected these days when they are smaller. However, smoking seems

to confer a much greater risk that the cancer may be more aggressive. Cessation of smoking seems to lower the risk."

Since these results were presented at a medical meeting, the data and conclusions should be viewed as preliminary until publication.

Source: Research presented at the American Urological Association's 2011 Annual meeting: www.aua2011.org; US News Health: Heavy Smoking Tied to Advanced Kidney Cancer. 2011: http://health.usnews.com/health-news/family-health/cancer/articles/2011/05/15/heavy-smoking-tied-to-advanced-kidney-cancer

Axitinib could boost progression-free survival in renal cell cancer, Phase III study suggests

The results of a recent Phase III trial carried out by Pfizer were announced at the 2011 ASCO annual meeting. Pfizer's VEGF receptor inhibitor axitinib was compared with sorafenib therapy for patients with advanced renal cell carcinoma.

The Phase III study looked at 723 patients whose disease had progressed after prior therapy with either sunitinib-containing regimens (54%), cytokine-based therapy (35%), temsirolimus or bevacizumab. These patients were randomized to receive either axitinib or sorafenib twice daily.

The results indicate that compared with sorafenib therapy, axitinib increased median progression-free survival time by 43% in the overall patient population. This increased survival from an average of 4.7 to 6.7 months.

In patients previously treated with sunitinib, progression-free survival was 4.8 months for those who were treated with axitinib compared with 3.4 months for those treated with sorafenib.

In patients previously treated with cytokine-based therapy, treatment with axitinib resulted in a median progression-free survival of 12.1 months, compared with 6.5 months for the sorafenib group.

The firm is now filing submissions for axitinib to regulatory authorities worldwide.

There is currently an ongoing Phase III trial investigating axitinib for treatment-naive renal cell carcinoma patients.

Source: Rini BI. Axitinib versus sorafenib as second-line therapy for metastatic renal cell carcinoma (mRCC): results of Phase III AXIS trial American Society of Clinical Oncology (ASCO) Annual Meeting. *Chicago, IL, USA (2011) (Abstract 4503).*

TKI treatment may improve overall survival and decrease metastasis in renal cell carcinoma patients

A retrospective study of metastatic renal cell carcinoma (mRCC) has compared patients treated with tyrosine kinase inhibitors (TKIs) with a non-TKI group.

The researchers from the Baylor College of Medicine investigated 338 patients with mRCC but no brain metastases. They found that the 154 patients treated with TKIs (46%), including sunitinib and sorafenib, had better overall survival than the non-TKI group of 184 patients (54%) and that the TKI patient group also encountered less-frequent metastasis to the brain.

The TKI-treated patient group were found to have a median overall survival of 25 months, whereas the non-TKI group had a median survival of only 12.1 months ($p < 0.0001$, hazard ratio of 0.53). The two groups had no difference in age, histology, nephrectomy or the sites of metastases.

A total of 44 patients developed brain metastases. However, 15.8% of the non-TKI group had metastatic cancer, compared with just 9.7% of the TKI-treated group.

Patients were identified from the institutional register and presented with renal cancer either between 2002 and 2003 or between 2006 and 2007. The researchers collected data on age, sex, Fuhrman grade, disease site, nephrectomy, systemic therapy including TKIs (sorafenib or sunitinib), Memorial Sloan-Kettering Cancer Center risk category, brain metastasis treatment and vital status. All of the above data was considered in the statistical analyses.

The authors concluded that treatment with TKI agents reduces the incidence of brain metastasis in mRCC.

Source: Verma J, Jonasch E, Allen P, Tannir N, Mahajan A. Impact of tyrosine kinase inhibitors on the incidence of brain metastasis in metastatic renal cell carcinoma. Cancer *DOI: 10.1002/cncr.26138 (2011) (Epub ahead of print).*

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