New biomarkers and treatment strategies in renal cell cancer

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Abstract

BACKGROUND

Renal cell cancer (RCC) is an aggressive type of cancer. Despite an increasing number of therapeutic options, the prognosis of patients with advanced RCC remains dismal. Sunitinib is a first line agent for treatment of patients with metastatic RCC. It induces disease stabilization or regression in most patients with RCC. Unfortunately, drug resistance inevitably occurs. Predictive “biomarkers” typically foretell which patient will respond to the therapy before start of treatment. This thesis aims to improve the treatment efficacy through development of predictive biomarkers. In order to overcome drug resistance, strategies that may improve the antitumor effects of sunitinib will be investigated.

METHODS

Mass spectrometry-based phosphoproteomics experiments have been conducted in preclinical cancer models to validate this technology for discovery of predictive biomarkers. Additional studies were performed using plasma and tissue samples from patients with cancer. The preclinical cancer models were also used in combination with the phosphoproteomics technology, a whole genome siRNA library and CRISPR/Cas9 genome editing to identify potential novel treatment strategies. A doxycycline-inducible shRNA model was used to test a potential combination treatment strategy in mice.

RESULTS
Mass-spectrometry of peptides, immunoprecipitated with the pTYR-1000 anti-phosphotyrosine antibody, allows identification of highly phosphorylated proteins in tumor tissue of patients with cancer. The specifications of the measurements, in terms of reproducibility and depth, in 14G needle biopsies are sufficient for biomarker studies in patients. Extracellular vesicles may allow non-invasive monitoring of protein phosphorylation in plasma, but technical advances are required to determine potential as biomarker platform. Furthermore, phosphoproteomics measurements in vitro highlighted activation of Axl signaling during sunitinib treatment. A functional genetic screen revealed the sunitinib sensitizing properties of CEP70 downregulation. Induction of TIGAR may represent an alternative strategy to sensitize tumors to sunitinib.

CONCLUSION

Phosphoproteomics measurements in needle biopsies from patients with RCC may yield biomarkers that predict the response to sunitinib. Drugs that interfere with Axl signaling, CEP70 expression or induce TIGAR may sensitize tumors to sunitinib.