Intratumoral heterogeneity of renal cancer is related to differences in drug response and development of therapy resistance

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Background and Aim

Patients with advanced renal cell carcinoma (RCC) have a poor prognosis not least because of resistance towards standard drugs. Recently, pronounced intratumoral heterogeneity (ITH) in RCC was shown. We were interested whether this ITH is a potential cause for treatment failure. We developed a large panel of patient-derived xenograft (PDX) models from RCC, including subsets of models from different regions of one individual patient tumor. The PDX models were evaluated for response to targeted standard therapeutics. To better understand correlations between inter- and intratumoral heterogeneity and treatment response, an explorative analysis of gene expression and panel sequencing data was performed.

Methods

Specimens from primary and metastatic RCCs were collected from consenting patients and transplanted into mice. Tumor engraftment was monitored for up to 4 months. Tumor sections were examined histopathologically to assess concordance between patient tumor and model and were stained for RCC-specific markers (Pax2, Pax8, CD31, and RCC). Stable growing PDX were treated with the targeted compounds bevacizumab, sunitinib, sorafenib, and everolimus. Genome-wide gene expression was analyzed using Affymetrix microarrays. In addition, sequence variations using the Illumina® NGS TSA cancer panel and MET and TERT gene copy numbers were analyzed in PDX models.

Results

A panel of 34 RCC PDX models was established from more than 200 patient samples. Among these, 13 models were derived from different tumor regions of three patients with advanced disease. Original patient tumor and PDX showed a very similar and characteristic RCC histopathology. Inter- and intratumoral heterogeneity was preserved for several passages. We treated all PDX with 4 standard targeted drugs and observed response rates comparable to results from clinical trials. One out of 8 regions obtained from one aggressive RCC (11175) clearly differentiated regarding its response to bevacizumab and sunitinib. Genomic analysis revealed that this region (11175D) has differences in global gene expression and mutational status. Besides a common MET mutation an additional variation in the HRAS gene was detected. Differential gene expression analysis of treatment responder/nonresponder groups resulted in weak sets of genes (low fold change) significant in moderated t-test but not significant after False Discovery Rate (FDR) adjustment, supposedly because of a constrained assessment of true responder groups. In the whole PDX set we found 34 sequence variations in 20 genes, e.g. ATM, MET, TERT and VH1 and copy number variations in the MET locus (CNV data not shown).

Conclusions

We have shown that PDX derived from distinct regions within one individual patient tumor can exhibit differences in genomic profile which possibly results in altered treatment response. This intratumoral molecular heterogeneity and its correlation to treatment response is subject of ongoing investigations to explain failure in renal cancer treatment. The available panel of renal cancer PDX provides an excellent source for translational research and for preclinical testing of new drug candidates.