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Genomic and Epigenomic Profiling for Target Discovery in Translocation Renal Cell Carcinoma

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Background

Translocation renal cell carcinoma (tRCC) is a rare and aggressive type of non-clear cell renal cell carcinoma (RCC) that represents 1-5% of sporadic RCC in adults and 20-75% of kidney cancers in children. Biologically, tRCC is driven by rearrangements involving a member of the MiT/TFE transcription factor family, most commonly TFE3. There are currently no molecularly-targeted therapies specific to translocation renal cell carcinoma (tRCC) and effective treatments for this aggressive cancer remain a major unmet medical need. A barrier to effective therapies in tRCC is an incomplete mechanistic understanding of precisely how MiT/TFE gene fusions exert their oncogenic function.

We have previously leveraged "histologic overlap" between tRCC and other RCC subtypes in order to identify tRCC cases from across multiple genomic, clinical trial, and retrospective datasets and to define the molecular landscape of this disease. In this study, we performed functional epigenomic profiling across an array of tRCC cellular models and intersected with our prior genomic data to nominate key pathways involved in driving tRCC.

Methods

From previously published datasets, we re-analyzed data from DNA-sequencing of 74 tRCC cases (profiled by either Whole Exome Sequencing, Whole Genome Sequencing, or gene panel sequencing) and RNA-sequencing of 46 tRCC cases. We also performed whole genome and transcriptome sequencing on a cohort of institutional tRCC cases. We performed chromatin immunoprecipitation and sequencing (ChIP-Seq) on a panel of tRCC and clear-cell RCC (ccRCC) cell lines, using antibodies against TFE3 as well as the active enhancer mark H3K27ac. Functional studies in cell lines were used to validate our epigenomic profiling results and to study the role of MiT/TFE fusions in driving a tRCC-specific transcriptional program.

Results

Transcriptional profiling of tRCC tumors revealed overexpression of genes implicated in the antioxidant stress response and NRF2 signaling compared to other forms of RCC. This was confirmed by epigenomic profiling and functional studies, which suggest multilevel transcriptionaland post-transcriptional regulation of NRF2 signaling by TFE3 fusions. In addition, tRCC cell lines demonstrated variable levels of NFE2L2 dependence in vitro. Signatures of NRF2 activation, which are enriched in tRCC, correlate with resistance to many targeted therapies, including agents used in the treatment of kidney cancer.

Conclusions

tRCC tumors and cell line models share an epigenetic and transcriptional profile characterized by activation of the antioxidant stress response and heightened NRF2 signaling. This program appears driven directly by TFE3 fusions, and may be responsible for poor responses to existing targeted therapies. Modulation of this pathway may a potential strategy for overcoming drug resistance in tRCC.

Keywords

Translocation renal cell carcinoma; genomics; TFE3; TFEB; MITF; NRF2; VEGFR; immune checkpoint inhibition; immunotherapy; oxidative stress

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Impact of race and payor status on patterns of utilization of partial and radical nephrectomy in patients with localized renal cell carcinoma (RCC)

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