Cumulative number of altered biomarkers in mTOR gene pathway is an independent predictor of outcome in patients with clear cell renal cell carcir
Abstract," by Oussama Darwish, MD and Vitaly Margulis, MD

Cumulative number of altered biomarkers in mTOR gene pathway is an independent predictor of outcome in patients with clear cell renal cell carcinoma, "Beyond the Abstract," by Oussama Darwish, MD and Vitaly Margulis, MD

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BERKELEY, CA (UroToday.com) - Delineating the genetic events contributing to the pathogenesis of clear cell renal carcinoma (ccRCC) has led to significant advances in our understanding of tumor biology and directly led to the development of targeted molecular therapy for this disease. The molecular event central to tumorigenesis in ccRCC is dysregulation of hypoxia inducible factor 1 (HIF-1). This results, in the majority of cases, from mutations in the von-Hippel Landau (VHL) gene which is responsible for degradation of HIF-1. Accumulation of HIF-1 causes increased transcription of target genes such as vascular endothelial growth factor (VEGF) culminating in increased angiogenesis and tumor cell proliferation.

Intricately related to HIF-1 signaling is the mammalian target of rapamycin (mTOR) gene pathway. mTOR activation results in the promotion of translation and elongation factors that result in increased translation of HIF-1 protein. The importance of the mTOR pathway in ccRCC has been underscored by the significant clinical benefit of mTOR inhibitors in advanced ccRCC. Temsirolimus, an mTOR inhibitor, was the first targeted agent shown to improve survival in patients with metastatic ccRCC.

The goal of our study was to examine the association of upregulation of the mTOR pathway with clinical outcomes of disease severity in patients with ccRCC. Our cohort consisted of 419 patients with non-metastatic clear cell renal cell carcinoma. All patients, 247 Men (59%) and 171 women (41%), had been treated for the kidney cancer with either radical or partial nephrectomies between 1997 and 2010. Eighty-six (20.5%) of the patients presented with non-organ confined (pT3-T4) disease and 131 patients (31%) had high Fuhrman grade (3-4) cancers.

We employed tissue microarray constructs and immunohistochemistry to determine expression of several components of mTOR signaling. Specifically, we quantified the expression of 9 markers including mTOR, phosphorylated mTOR (p-mTOR), HIF-1A, and RAPTOR (an mTOR co-regulatory protein), as well as upstream (PTEN, AKT, p-AKT, PI3K) and downstream (p-4EBP1, p-S6) targets of mTOR signaling.

The cohort was stratified into low, intermediate or high risk groups according to the number of markers that demonstrated positive expression (low risk ≤ 3 markers, intermediate risk = 3 to 4 markers, and high risk ≥ 5 markers). Kaplan-Meier survival analysis found a significant correlation between the risk stratification categories and disease recurrence. Those falling into the low- to intermediate-risk groups demonstrated a hazard ratio of 3.8 ($p = 0.05$) while those in the high-risk category demonstrated a hazard ratio of 7.9 ($p = 0.001$). After controlling for tumor stage and grade, the high marker score (≥ 5 markers) on multivariate Cox regression analysis was found to be an independent predictor of recurrence (HR = 3.3, $p = 0.01$).

Therefore, expression of the markers studied was significantly correlated to disease severity. The greater the number of biomarkers that were aberrantly expressed, the worse the oncologic outcomes. This study adds to the growing body of evidence that up-regulation of the m-TOR pathway is a negative prognostic indicator in ccRCC. Stratification by the marker panel employed in this study allows improved prognostication in patients with ccRCC. Such stratification based on cumulative marker expression may augment current risk stratification tools in kidney cancer. For example, a patient's marker profile could be determined by

percutaneous biopsy, and if unfavorable could signify a tumor that would be more appropriately treated with surgical or ablative therapy as opposed to active surveillance. Although this tumor marker panel needs to be validated in prospective studies, our study ›vides further evidence that dysrgegulation of the mTOR pathway holds useful clinical utility in prognostication and management renal cell carcinoma.

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Oussama Darwish, MD[a] and Vitaly Margulis, MD[b] 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.

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More Information about *Beyond the Abstract*

Tags: **clear cell renal carcinoma (ccRCC)** **hypoxia inducible factor 1 (HIF-1)** **mammalian target of rapamycin (mTOR)** **vascular endothelial growth factor (VEGF)**

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Stone D
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BPH
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