

# Tumor-infiltrating regulatory T lymphocytes orchestrate oncogenic PAK1-conferred immune evasion in clear-cell renal cell carcinoma

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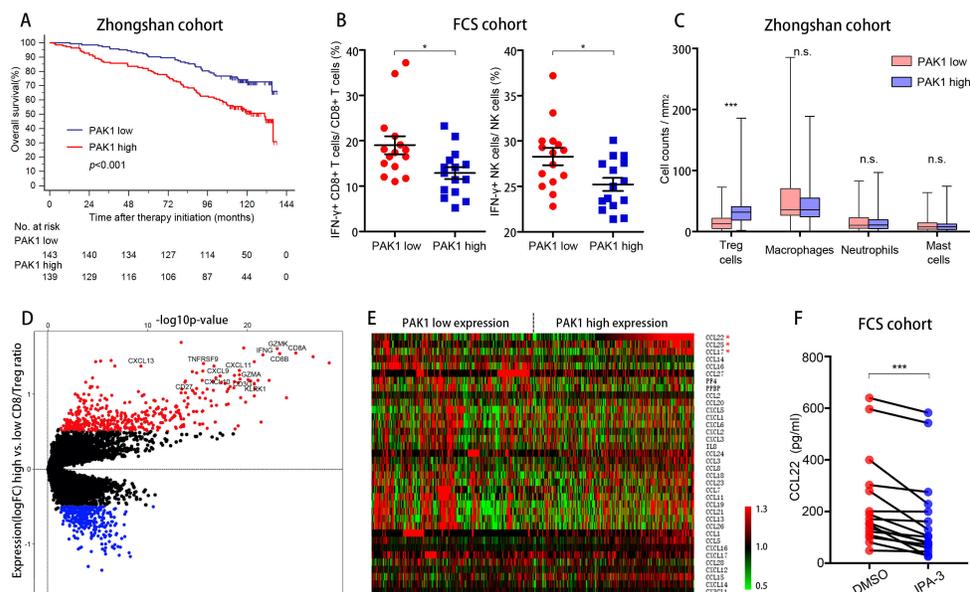
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**Introduction & Objectives:** Little is known about the associations between PAK1 and anti-tumor immunity in clear-cell renal cell carcinoma (ccRCC). This study aims to explore the prognostic value of PAK1 in ccRCC patients and investigated the molecular immune mechanism for its oncogenic role.

**Materials & Methods:** We retrospectively enrolled 282 ccRCC patients undergoing nephrectomy between 2005 and 2007 in Zhongshan hospital. Immunohistochemistry evaluated PAK1, CCL22, FOXP3 and CD8 expression in clinical specimens. Fresh tumor tissues, para-tumor tissues and peripheral blood for RT-PCR, ELISA, flow cytometry analyses were collected from patients who underwent nephrectomy in Zhongshan Hospital from September 2017 to April 2018. We compared clinical outcomes by Kaplan-Meier survival analysis and Cox regression model. Bioinformatics analysis performed in TCGA KIRC cohort.

**Results:** High PAK1 expression indicated poorer overall survival (OS) and recurrence free survival (RFS) (both  $p < 0.001$ ) in ccRCC patients. Multivariate analyses indicated PAK1 as an independent prognostic factor. PAK1 clearly correlated with immunosuppressive microenvironment in ccRCC tissues. In clinical samples, PAK1 positively correlated with Treg cells. IL-10<sup>+</sup> and TGF- $\beta$ <sup>+</sup> Treg cells both increased in PAK1<sup>high</sup> tumors. Additionally, CCL22 was highly secreted in PAK1<sup>high</sup> tumors. After treated by IPA-3, CCL22 secretion was clearly inhibited ( $p < 0.001$ ). Finally, we built a nomogram to predict OS for ccRCC patients with higher predictive accuracy.



**Conclusions:** Increased PAK1 expression predicted dismal prognosis in ccRCC patients by inducing tumor immune escape. IL-10<sup>+</sup> and TGF-β<sup>+</sup> Treg cells recruited by CCL22 play a dominant immunosuppressive role in PAK1<sup>high</sup> tumors.

