KIDNEY CANCER

Invading immune-cell phenotypes correlate with recurrence risk

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Following the introduction of immune-checkpoint inhibitors, durable long-term responses have been observed in subsets of patients treated with these therapies. Thus, considerable interest has emerged in the role of the infiltrating immune cells in cancer and the potential prognostic implications of the specific immune infiltrates and microenvironments of individual cancers. Now, the findings of research conducted by Nicolas A. Giraldo, with Catherine Sautès-Fridman and Wolf H. Fridman, reveal the identity of specific tumour-infiltrating lymphocytes (TILs) that indicate a high risk of recurrence following nephrectomy in patients with clear cell renal cell carcinoma (RCC).

On the rationale for this approach, Sautès-Fridman explains: “Our group previously demonstrated that patients with the highest risk of disease progression have a tumour microenvironment enriched in exhausted T cells and low densities of functional mature dendritic cells”, in another study: “we found that patients with RCC

with the lowest response rates to sunitinib and the shortest survival durations have the highest expression of genes related to T-cell exhaustion.”

Primary tumour samples were collected from a total of 40 patients with RCC undergoing partial or radical nephrectomy, in addition to preoperative peripheral blood samples and adjacent nonmalignant kidney tissue samples from the majority of patients. Tumour samples were homogenized and the expression of a variety of immune-cell markers of inhibition, including PD-1 and CTLA-4, and activation, including CD38 and CD40L, was investigated using multiparametric flow cytometry.

These analyses revealed three dominant TIL profiles: immune-regulated tumours, as observed in 22% of the cohort, characterized by T cells that coexpress the immune checkpoint proteins PD-1, Tim-3 and Lag-3, with enrichment of CD4⁺ICOS⁺ regulatory T cells (T_{reg}); immune-activated tumours, also observed in 22% of the cohort, with increased

levels of CD8⁺PD-1⁺Tim-3⁺TILs; and immune-silent tumours, which were present in 56% of the cohort, and had few detectable TILs.

Patients with immune-regulated tumours also had aggressive histological features, including inflammation, and had the shortest median disease-free survival durations following nephrectomy (median disease-free survival duration 7 months versus not reached in patients with immune-activated, or immune-silent tumours).

These findings, albeit from a small cohort of patients, indicate that patients with immune-regulated tumours, which are characterized by histological signs of inflammation and infiltration with TILs expressing several immune-checkpoint proteins and enrichment of CD4⁺ICOS⁺T_{reg}, have an inferior prognosis, and might benefit from treatment with adjuvant therapy and/or immune-checkpoint inhibition.

Sautès-Fridman summarizes: “This work helps to explain the aggressive behaviour of certain early stage tumours and unravels relevant questions in tumour immunology, such as how CD8⁺ TIL infiltrates can be associated with poor prognosis in some cancers”. On the future directions of this research, she adds: “First, we aim to extend this analysis to a greater number of patients. Second, ways have to be found to identify patients with a high risk of disease progression in the year following nephrectomy using easier and more widely available techniques (including validation of a smaller set of markers), and to circumvent the need for relative-clustering analyses.”

Peter Sidaway

ORIGINAL ARTICLE Giraldo N. A. et al. Tumor-infiltrating and peripheral blood T cell immunophenotypes predict early relapse in localized clear cell renal cell carcinoma. *Clin. Cancer. Res.* <http://dx.doi.org/10.1158/1078-0432.CCR-16-2848> (2017)