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KIDNEY CANCER

Orchestration of immune checkpoints has prognostic value in ccRCC

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New research published in *Clinical Cancer Research* has identified new independent prognostic factors in the tumour microenvironment of primary and metastatic clear cell renal cell carcinoma (ccRCC), which could guide the selection of patients who are likely to respond to checkpoint blockade therapies.

Giraldo *et al*. investigated the infiltration and localization of CD8-positive T cells and mature dendritic cells in a cohort of 135 primary ccRCC tumours and 51 ccRCC lung metastases, in relation to prognosis. The expression of immune checkpoints (including PD-1, LAG-3, PD-L1 and PD-L2) were also analysed.

> “...expression of immune checkpoints can modulate the clinical effect of CD8-positive cells...”

In primary ccRCC, the density of CD8-positive T cells in the invasive margin of the tumour was heterogeneous. Using the Optimal P value (OPv) cut-off point for disease-free survival (DFS) (630 cells/mm^2) the cohort of patients with tumours containing high numbers of CD8-positive T cells (CD8^{High}) had significantly shorter DFS and overall survival (OS) than those with tumours containing low numbers of CD8-positive T cells (CD8^{Low}) ($P = 0.0001$ and 0.001, respectively).

Expression of the immune checkpoint proteins PD-1, LAG-3, PD-L1 and PD-L2 was able to identify patients with poor clinical outcome. Patients with tumours that were considered to be PD-1^{High} or LAG-3^{High} in the invasive margin, or which contained cells that were PD-L1 or PD-L2 positive, had shorter DFS and OS. However, the density of PD-1-positive or LAG-3-positive cells in the tumour centre was not significantly associated with prognosis. Patients who had PD-1^{High} lymphocytes in the invasive margin and also had PD-L1-positive and/or PD-L2-positive tumour cells had the worst prognosis, with 6.1-fold higher risk of progression after resection.

For lung metastases, patients with CD8^{High}, PD-1^{High} or LAG-3^{High} tumours also had significantly shorter OS. The expression of PD-L2 on metastatic tumour cells was associated with worse clinical outcome, but PD-L1 expression was not. Combined expression of PD-1, PD-L1 and PD-L2 identified patients at high risk of progression.

Analysis of a confirmation cohort of 496 primary ccRCC tumours from The Cancer Genome Atlas revealed that expression of seven genes, associated with a T helper cell and CD8-positive cell response, correlated with poor prognosis. Of these seven genes, *IFNG* displayed the lowest *P* value ($P = 3.17 \times 10^{-7}$) and patients who had high intratumoral expression of *IFGN* had significantly shorter OS ($P = 0.006$). Expression of *IFGN* showed significant positive correlation with both PD-L1 and PD-L2.

These results indicate that the expression of immune checkpoints can modulate the clinical effect of CD8-positive cells in ccRCC. Thus, the immune profiles of patients could aid clinicians in selecting those with ccRCC who are likely to respond to immunotherapies.

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Original article Giraldo, N. A. *et al*. Orchestration and prognostic significance of immune checkpoints in the microenvironment of primary and metastatic renal cell cancer. *Clin. Cancer Res*. doi:10.1158/1078-0432.CCR-14-2926