EXPLORING THE MICROENVIRONMENT OF CLEAR CELL RENAL CELL CARCINOMA TO IMPROVE THERAPY WITH TUMOR INFILTRATING LYMPHOCYTES


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Background Improving the long-term efficacy of treatments for advanced renal cell carcinoma (RCC) beyond first-line therapy remains a significant challenge. Adoptive cell therapy (ACT) utilizing tumor infiltrating lymphocytes (TIL) has emerged as a promising personalized immunotherapeutic approach for solid tumors. Nevertheless, the RCC tumor microenvironment presents considerable obstacles for the successful application of TIL therapy. Consequently, the aim of this study is to investigate the tumor microenvironment in RCC to predict TIL growth outcomes and their reactivity.

Methods Tumor fragments collected from 43 patients with clear cell RCC (ccRCC) were cultured for 4 weeks in media supplemented with high dose IL-2 (6000 IU/mL). At the end of the 4 weeks, TIL were further expanded using a rapid expansion protocol (REP). Pre- and post-REP TIL expansion was assessed, the memory phenotype and expression of activation and co-inhibitory markers were evaluated by flow cytometry, and reactivity to autologous tumor was assessed by IFN\(\gamma\) secretion. The remaining tumor tissue (n=10) was enzymatically digested into a single cell suspension, and immune cells within the tumor microenvironment were evaluated by flow cytometry.

Results From ccRCC tumors, 88.6% resulted in successful TIL expansion, yielding a mean of 8.72e7 TIL per fragment. Pre-REP reactivity against autologous tumors was high, with 76.4% of the samples demonstrating complete reactivity, 17.7% showing partial reactivity, and only 5.9% not showing any reactivity. The T cell phenotypes in expanded TIL trended towards more CD4+ than CD8+ T cells. All fragments that underwent REP were able to expand with a mean expansion rate of 92-fold. The tumor microenvironment was composed of 73.6% of immune cells (CD45+), with 71.2% of T lymphocytes, 3.3% of B cells, and 1% of Natural Killer (NK, CD3-CD56+) cells. Among the lymphocyte population, 41.7% were CD8+ and 45.8% were CD4+. Within the CD8 population, 52.8% displayed an effector memory phenotype (CCR7-CD45RA-), and 23.8% were terminally exhausted (CD69+CD39+TOX+). A positive correlation was found between the percentage of expanded fragments and the percentage of CD4 T cells, NK cells, and naïve CD8 T cells (CCR7 +CD45RA+CD95-) within the initial tumor samples.

Conclusions These results demonstrate the feasibility of expanding tumor-reactive TIL from ccRCC, despite the presence of terminally exhausted CD8+ T cells in the tumor microenvironment. Moreover, this study provides valuable insights into the tumor microenvironment of ccRCC and its impact on TIL growth outcomes. Understanding the complex interplay between the tumor microenvironment and TILs is crucial for optimizing ACT strategies.

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