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Creation of Human Assembloids Recapitulating Epithelial-Stomal Interaction in Human Cancer

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Title: Tumor-induced, CAFs-dependent exhaustion of cytotoxic T cells through FGF2/WNT5A signaling axis in renal cell carcinoma

Cellular interplays between cancer cells and their microenvironment affect the pathophysiology of human cancers including tumor dynamics and heterogeneity as well as drug responses. However, the nature of those interactions at the cellular level remains elusive due to the lack of relevant model system that recapitulates tumor-stromal interactions of human tumors. Here, we created human tumor assembloids by reconstituting patient-matched tumor cells, cancer-associated fibroblasts (CAFs), and CD8+ cytotoxic T cells from patients with renal cell carcinoma. These tumor assembloids recapitulate dynamic interactions between tumor cells, CAFs, and immune cells of patient tumors, and are capable of representing the patients' responses to the immunotherapeutic agents such as anti-PD-1 antibody. Using genetically manipulated, combinatorial tumor assembloids combined with humanized mouse model, we found that the increased expression of FGF2 in tumor propagating cells (CA9+) elicits stromal expression of WNT5A from CAFs, which in turn drives the exhaustion of cytotoxic T cell and subsequent resistance to checkpoint inhibitors in tumors derived from non-responsive patients. Interestingly, initial activation of CD8+ T cells, which is mediated via FGF2/WNT5A signalling axis between CA9- tumor and CD8+ T cells, is maintained in both responsive and non-responsive tumors, suggesting that CAF-mediated T cell dysfunction is independent of the T cell activation process, and rather develops at the later stage of T cell exhaustion in non-responsive patients. Pharmacological blockade of signaling axis between tumor cells, CAFs and cytotoxic T cells furthermore dramatically increases the responsiveness to anti-PD-1 treatment of non-responsive tumors, suggesting an approach to management of non-responsive patients to immunotherapy.

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