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Clinical successes in cancer immunotherapy, including immune checkpoint blockades and chimeric antigen receptor T cells, have settled a long-debated question in the field: whether tumors can be recognized and eliminated by our own immune system, specifically, the T lymphocyte. Meanwhile, current limitations of these advanced treatments pinpoint fundamental knowledge deficits in basic T cell biology, especially in the context of tumor-carrying patients. Aiming to develop new immunotherapies against cancers, and interconnected with clinical trials executed by clinician collaborators and immunogenomic tools developed in house, my research program rests on three pillars – the T cell, the Tumor Microenvironment, and Immunotherapy.

We regard the tumor as an acquired immunosuppressive organ. By this scientific precept, we study how tumors inhibit T and NK cells-mediated immunity both locally and systemically. Our early TCR repertoire profiling of gastric tumors and tumor-free patient mucosa revealed the correlation between tissue resident T cell diversity and patient survival. Our recent single cell RNA sequencing study depicted complex pathways to develop T cell memory intratumorally. Currently, aided by bioinformatics, animal models and clinical cohorts, we are actively dissecting signaling pathways, transcription regulatory networks, and epigenetic programs governing T and NK cell differentiation in the tumor microenvironment. Moving beyond the local microenvironment, our previous studies also demonstrated that tumors remotely modulate T cell mediated immunity at every step: priming, trafficking, and intratumoral function. Our in-depth investigation unveiled the profound impact of this “tele-education”: established tumors hijack hematopoiesis to protect themselves against T cell surveillance. The next step is to develop clinically feasible strategies counteracting tumors-biaed systemic immune suppression.

The expanding boundary of T and NK cell biology is the frontier of cancer immunotherapy. The contrast between the unprecedented success of T cell-based therapies for blood malignancies and their repeated failures against solid tumors vividly highlights our prevalent challenges: to understand how T cells can infiltrate tumors; how infiltrated T cells can resist microenvironmental suppression; and how activated T cells can form persistent memory to restrict tumor development and metastasis. As a general principle, we believe that it is necessary to empower CAR-T or TCR-T cells with enhanced functionality against solid tumors. We also believe the NK cell is a promising platform to integrate genomic engineering for shelf-ready immune cell therapy. Currently, we are actively involved in such armored CAR-T/CAR-NK or TCR-T/TCR-NK trials for various solid tumor treatments.

Accompanying these trials, and other immunotherapies carried out by colleagues world-wide, we design and execute comprehensive immune monitoring procedures to rationalize successes and failures. Clinical observations are smoothly deconstructed into basic but intriguing T/NK cell questions for us to answer, and answers generated on the bench directly inform cell drug designs in future trials. This is our closed circle of research and day-to-day operation.