Underlying mechenisms of myeloid-targeted immunotherapies revealed by single-cell analyses in colorectal cancer

With support of the National Natural Science Foundation of China and the Chinese Academy of Sciences, a collabration team led by Prof. Zhang ZeMin (张泽民) from the Biomedical Pioneering Innovation Center, School of Life Sciences at Peking Univeristy, Peking-Tsinghua Center for Life Science and Beijing Advanced Innovation Center for Genomics, uncoverd the underlying mechnisms of myeloid-targeted immunotherapies by single-cell analyses, which was published in *Cell* (2020, 181(2): 442—459. e29).

Tumor-infiltrating myeloid cells are a heterogeneous population of mononuclear phagocytes and granulocytes. Although accumulating studies have revealed their contributions to modulating tumorigenesis and progression, much remains to be understood about the detailed characteristics of these cells and how they interact with tumor-infiltrating T cells and stroma cells to shape the tumor microenvironment (TME).

Regarding colorectal cancer (CRC), recent clinical trials have demonstrated that patients with microsatellite instability (MSI) show better responses to immune-checkpoint blockade (ICB) treatment than those with microsatellite stability (MSS), however, the underlying mechanisms are less understood. Therefore, Zhang's group had initially utilized scRNA-seq to evaluate T cell subsets in the blood, adjacent normal mucosal, and tumor compartments from CRC patients, identifying dynamic relationships between T cells by a newly developed analysis framework, STARTRAC. Importantly, they uncovered the intriguing association between *BHLHE40*$^+$ Th1-like cells and MSI CRC patients, providing a rationale for the high response rate to ICB in these patients. These valuable findings have been published in *Nature* previously.

Given that T cell-based ICB has shown variable activity in different cancer patients as aforementioned, additional therapeutic strategies to potentiate anti-tumor immunity have been proposed, including those blocking tumor-associated macrophages (TAMs) and activating dendritic cells (DCs). A comprehensive understanding of the heterogeneity of these cells can facilitate the selection of strategies being advanced to the clinic based on clear mechanistic hypotheses. For this purpose, Zhang's group performed combined single-cell analyses on the TME in CRC patients and murine tumor models. In addition to mapping various tumor-infiltrating myeloid cell subsets and identifying their respective signature genes, they successfully deduced a cell-cell interaction network in human CRC, identifying specific TAM and conventional DC (cDC) subsets as key mediators of cellular cross-talk. Through systematic comparison, they identified analogous immune cell subsets in pre-clinical mouse tumor models in the context of therapies in clinical trials, including anti-CSF1R and anti-CD40 treatment. Interestingly, anti-CSF1R blockade treatment selectively depleted pro-inflammatory TAM populations, such as *C1QC*$^+$ TAMs, but spared pro-angiogenic *SPP1*$^+$ TAMs, providing a previously unrecognized mechanism for tumor resistance to such treatment. By contrast, anti-CD40 agonist treatment preferentially activated *Ccl22*$^+$ cDC1 population and increased *Bhlhe40*$^+$ Th1-like and CD8$^+$ memory T cells. Together with previous finding of *BHLHE40*$^+$ Th1-like cells in MSI CRC patients (*Nature*, 2018), these observations suggest that anti-CD40 treatment may promote response to ICB in otherwise non-responding CRC patients. Collectively, this study demonstrates the translatability of myeloid modulating therapies from pre-clinical models to human cancer, providing a new paradigm for dissecting underlying mechanisms of other therapeutic strategies.

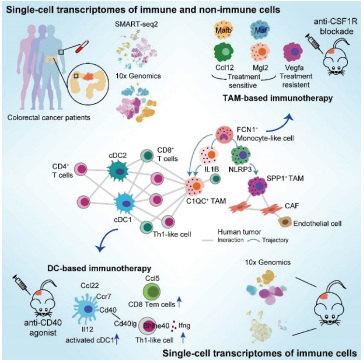

Figure Mechanisms of TAM— and DC-targeted immunotherapies revealed by combined single-cell analyses.