A DETAILED VIEW OF DISEASE MECHANISMS

Using single-cell technologies, BIOPIC researchers have improved disease treatment.

Xie's single-cell technologies locate neutralizing antibodies against SARS-CoV-2 to block its entry into host cells.

Advances in single-cell technologies are shaping the future of biology. New methods have allowed researchers to gather and analyse information on genome structure and functions from individual cells, one at a time, providing new insights into diseases. Harnessing single-cell technologies, researchers at BIOPIC have revealed the mechanisms of some of the most devastating diseases, from cancer to infectious diseases, informing treatment strategies.

Understanding tumour microenvironment

Tumour immune microenvironment affects tumour initiation and response to therapy. However, this has been poorly understood, particularly for liver cancer. A team led by BIOPIC researcher, Zemin Zhang, has characterized T cells in this common cancer, showing the tumour microenvironment immune landscape at the single cell level.

"We want to use the most detailed method to describe the compositions, functions, and dynamic changes and relationships of various types of cells in cancer," says Zhang. "This will facilitate molecular typing of cancer and devising treatment strategies for patients."

Single-cell RNA sequencing has enabled Zhang's team to simultaneously analyse more than 5,000 single T cells, isolated from peripheral blood, tumour, or normal tissues, revealing their distinct functional composition, along with their transcriptomes. Using the data, researchers identified 11 T cell subsets, along with their signature genes, based on molecular and functional properties, and outlined their developmental trajectories. Particularly, they found that many of the T cells in tumours are in a state of dysfunction, allowing tumours to evade immune surveillance.

More recently, combining two single-cell RNA sequencing technologies, the team extended their exploration to broader immune cells from various tissues in liver cancer patients. Here, they systematically compared their profiles, traced the dynamics of immune cells in liver cancer, including how they develop, interact, and migrate, adding new dimensions to the tumour immune landscape.

Zhang expects biological insights provided by his research to help identify novel therapeutic targets, as well as biomarkers for studying responses to current immunotherapies.

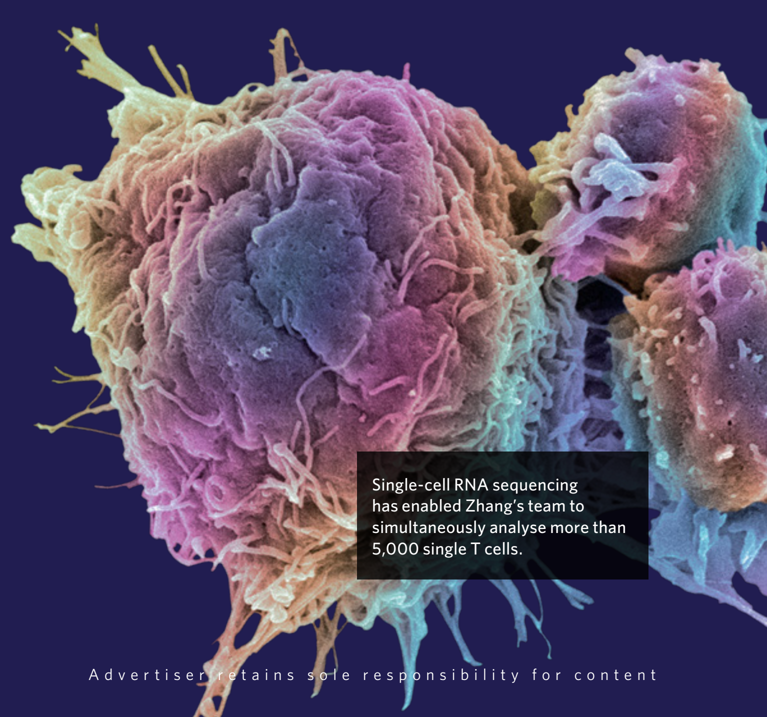
Seeking COVID-19 treatment

Single-cell technologies are also being harnessed in an effort to treat COVID-19. "Our strategy was to find neutralizing antibodies against SARS-CoV-2 from the blood of recovering COVID-19 patients, which could block virus entry into host cells," says Xiaoliang Sunney Xie, BIOPIC's director.

High-throughput single-cell sequencing techniques have significantly accelerated the work of Xie's group. In a July *Cell* paper, they reported finding 14 potent neutralizing antibodies by sequencing B cells from 60 recovering patients. One antibody, called BD-368-2, exhibited particularly high therapeutic and prevention efficacy in mouse models.

To better understand how neutralizing antibodies work, the team further explored the molecular mechanisms of BD-368-2. Xie's colleagues, Xiaodong Su and Junyu Xiao, revealed its high-resolution structure, and showed that BD-368-2 blocks recognition by ACE2, the protein acting as the receptor for the SARS-CoV-2 virus, by occupying all three receptor-binding domains simultaneously. They also found another antibody that, when paired with BD-368-2, can prevent escape from neutralizing antibodies by the virus spike protein variants, a cause for drug resistance.

"We are excited about the therapeutic potential of our neutralizing antibody candidate," says Xie. "It's always my goal to find clinical application of our single-cell technologies." ■



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