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The rapid development of analytical cellular tools has had a groundbreaking effect on scientific discovery in recent decades. Using newly available technologies such as next-generation sequencing (NGS), scientists have been racing to work out how genetic information can help to create treatments for major diseases, such as cancer. The advent of single-cell RNA sequencing has made it possible to analyze the transcriptomes of individual cells.

Yet single-cell technologies can only tell scientists so much, says immunologist Charlotte Scott of the VIB-UGent Center for Inflammation Research in Ghent, Belgium. Newly developed spatial biology technologies are the missing piece of the puzzle. Allowing specific cell types to be mapped locally within the tissue enables the investigation of biologically relevant cell-cell interactions based on spatial proximity, she says.

Scott’s work focuses on understanding the specific functions of macrophages, which are large white blood cells in the liver. “To fully understand these cells, we need a thorough understanding of both their heterogeneity and the local microenvironments of each subtype,” she says.

The advent of spatial biology was enabled by iterative rounds of technology innovation and scientific discovery, according to a recent white paper (resolve-biosciences.com/science) published by Resolve Biosciences. Affordable predecessor technologies such as microscopy and NGS showed the value of capturing the heterogeneity of cell populations, but did not provide in situ context. Spatial biology was the natural next step. This technology pairs the benefits of single-cell analysis with a view of natural tissue architecture based on recent advances in imaging technology, according to the report.

Spatial biology in itself is not a new concept, says Scott. “Researchers have been using confocal microscopy and immunohistochemistry to locate their cells of interest for decades. However, this has always been limited in terms of the number of parameters that could be assessed simultaneously. This has prevented the study of their interactions with other cells in the same microenvironment,” she explains.

Scott and her colleague Martin Guillaums at VIB-UGent have been working together on the Liver Cell Atlas project to generate the first spatial proteogenomics atlas of healthy and diseased livers in mice and humans. He believes their project will facilitate the high-throughput screening of a whole range of transgenic mouse models and large patient cohorts, which will lead to a better understanding of how these cells are affected in disease without the need for expensive single-cell RNA sequencing.

Different spatial technologies have been benchmarked at VIB thanks to the institute’s initiatives, such as Tech Watch and the Single-Cell Accelerator program. These advancements allow the Scott and Guillaums teams to select the best techniques and combine complementary spatial transcriptomics approaches to unravel the location of different macrophage subsets in specific microenvironments. First, the team determines cellular distribution within the tissue and narrows down the cells of interest in a specific zone. They then use Resolve Biosciences’ Molecular Cartography platform to study the most relevant cell-cell interactions within that zone at single-cell resolution.

Scott and Guillaums say that in recent years it has become clear that the local environment in which a cell resides greatly influences its phenotype and function. Thus, by understanding the spatial arrangement of cells in a tissue, scientists stand to gain significant insight into the factors regulating the functional specialization of cells and may ultimately identify the local cues that control cell activation.

They predict that further advances in spatial biology techniques, such as the combination of protein and RNA analyses, could help scientists find ways to control the development, activation, or inhibition of cells that play fundamental roles in human diseases.
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