'Multi-omics' adds new cell to immune family tree

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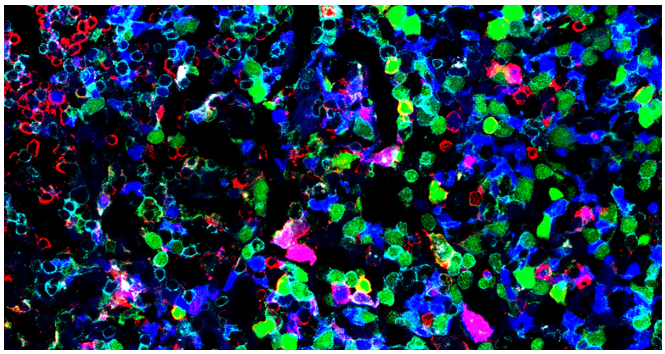

Australian researchers have used powerful 'single cell multi-omics' technologies to discover a previously unknown ancestor of T and B lymphocytes (pictured), which are critical components of our immune system. Credit: WEHI, Australia

WEHI researchers have used powerful 'single cell multi-omics' technologies to discover a previously unknown ancestor of T and B lymphocytes, which are critical components of our immune system.

Using an approach akin to breaking a sports team's performance down to the individual player statistics, the researchers looked at multiple aspects of single developing immune cells to define which cells would only give rise to T and B lymphocytes. This revealed a new stage in lymphocyte development, information which could enrich future studies of the immune system. The discovery has also led to new research opportunities, with WEHI establishing of one of Australia's first dedicated and integrated single cell research platforms in 2018, which is now being used to solve other research questions.

The research, which was published in *Nature Immunology* today, was led by Dr. Shalin Naik, Dr. Daniela Zalcenstein, Mr Luyi Tian, Mr Jaring Schreuder and Ms Sara Tomei.

Focussing on single cells

Our immune system comprises many different types of cells with different functions, but all immune cells are derived from a single type of cell, a blood stem cell. The development of different immune cell types occurs through a branching 'family tree' of immature cells. At earlier stages of immune cell development, individual cells can give rise to several different types of mature cell, but as development progresses, cells become more limited in which final mature cells they can produce.

T and B lymphocytes—which are critical for targeted, specific immune responses—are closely related immune cells, meaning they share many common steps in their development, said Dr. Naik. "Decades of research have defined how T and B lymphocytes develop, and the 'branch points' in their family tree when the developing cells lose the capacity to develop into other immune cell types," he said.

Dr. Zalcenstein said that to gain new insights into questions such as how immune cells develop, the team established Australia's first 'single cell multi-omics' platform, which is now available to all researchers within the Single Cell Open Research Endeavour (SCORE) established by Dr. Naik and Dr. Zalcenstein in collaboration with Dr. Stephen Wilcox of WEHI's Genomics Hub and Associate Professor Matthew Ritchie.

"Multi-omics technologies combine different biological data sets—such as genomics, transcriptomics and proteomics—to compare different samples in more detail than is possible by looking at one data set. We have applied this approach to study individual cells, in this case developing immune cells, to understand in more detail which cells can give rise to lymphocytes. This approach is called single cell multi-omics," she said.

"Rather than looking at data combined from many

cells in a sample, we focus in on individual cells to understand the differences that exist within a larger population. It's like looking at a football team—you can average out the number of goals, tackles and kicks per player in a game, but if you look at individual player statistics, you may discover that one player scored lots of goals, while another player was responsible for most of the tackles," she said.

A new lymphocyte progenitor

SCORE's study of immune cell precursors revealed a previously unrecognised cell type that could give rise to T and B lymphocytes, but not other immune cells.

"This cell occurred much earlier in lymphocyte development than we had suspected," Dr. Naik said. "Previous techniques had grouped different immune progenitors together, but by studying individual cells we were able to identify one cell type that was committed to developing into T and B lymphocytes."

The discovery adds a new layer to the family tree of T and B lymphocytes and could provide a boost to other areas of research.

"Understanding in more detail how T and B lymphocytes develop could lead to better approaches to regenerate these cells as a treatment for certain diseases," Dr. Naik said. "We also know that many types of leukaemia arise from defects in early stages of immune cell development, so we are curious to know whether this progenitor cell has links to any forms of leukaemia."

Dr. Zalcenstein said the research was an excellent example of the power of single cell multi-omics. "Lymphocyte development has been studied in great depth for at least four decades. Even so, by applying this new approach we were able to learn more about it. This was one of the first projects tackled by SCORE, and since then we have applied the same approaches to more than 100 different research questions. It's a really exciting new field to be part of," she said.

More information: A new lymphoid-primed progenitor marked by Dach1 downregulation identified with single cell multi-omics, *Nature Immunology* (2020). DOI: 10.1038/s41590-020-0799-x , www.nature.com/articles/s41590-020-0799-x

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