Immunology meets single-cell sequencing

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Research from the Single-Cell Genomics Centre on the Wellcome Genome Campus could change the way we look at gene expression and immune response. Published in *Nature Methods*, the new method, TraCeR, provides a powerful tool for research into immune response, vaccination, cancer and autoimmunity.

What makes one T cell attack an antigen, and another remember it for next time? A series of RNA sequencing experiments by the Teichmann group at the European Bioinformatics Institute (EMBL-EBI) and the Wellcome Trust Sanger Institute led the group to develop a new technique for understanding T-cell receptors. TraCeR, a single-cell sequencing tool, allows the determination of both the sequence of the T-cell receptor in individual cells, along with each cell's gene expression profile. This opens up new possibilities in the future for developing rapid diagnostics based on the genetic profile of blood cells.

When your immune system detects an invader - whether that's a disease or, in the case of autoimmune disease, part of your own body - it starts producing an army of T cells to remove the pathogen, which itself is producing lots of different proteins.

"It's a battlefield, with fighters on different fronts, snipers, generals and even journalists bearing witness," explains Mike Stubbington of EMBL-EBI, now at the Sanger Institute. "What we wanted to know was how different populations of T cells respond to disease - what role they're playing in the battle."

T cells are equipped with receptors that can latch on to a particular invader out of a vast array of possible options. This means they are extremely variable, with hundreds of billions of possible DNA sequences. A combination of paired sequences determines what protein a receptor will detect, so to understand what is happening at the molecular level, it is imperative to find both sequences in each cell. Using TraCeR, scientists can look at the DNA and RNA (expression) profiles of these highly variable T-cell receptors at the same time.

The researchers found the receptor sequences are unique, unless the T cells have the same parent cell. The presence of 'sibling' cells proves that an infection has triggered the division of a particular T cell, which indicates it is multiplying to fight the invader. Using TraCeR, the researchers accurately identified 'sibling' cells and explored their different response to Salmonella infection.

"This technique helps us see whether all the 'children' of a particular T cell do the same thing at the same time, which is an open question in biology," adds Tapio Lönnberg of EMBL-EBI. "We can start to see whether the antigen itself plays a role in how a T cell will respond, and even whether it's possible to determine what the invader is, just based on the sequence of a T-cell receptor."

"This kind of breakthrough work can only be done using single-cell measurements," says Sarah Teichmann, Head of Cellular Genetics at the Sanger Institute. "This new tool for single-cell sequencing gives us a new approach to the study of T cells, and opens up new opportunities to explore immune responses in disease, vaccination, cancer and autoimmunity."

The next step for the team is to apply similar methods to the study of B cells to better understand the adaptive immune system as a whole.

More information: T cell fate and clonality inference from single-cell transcriptomes, *Nature Methods*, DOI: 10.1038/nmeth.3800