Latest genomic technology uncovers secrets of immune system's response to malaria

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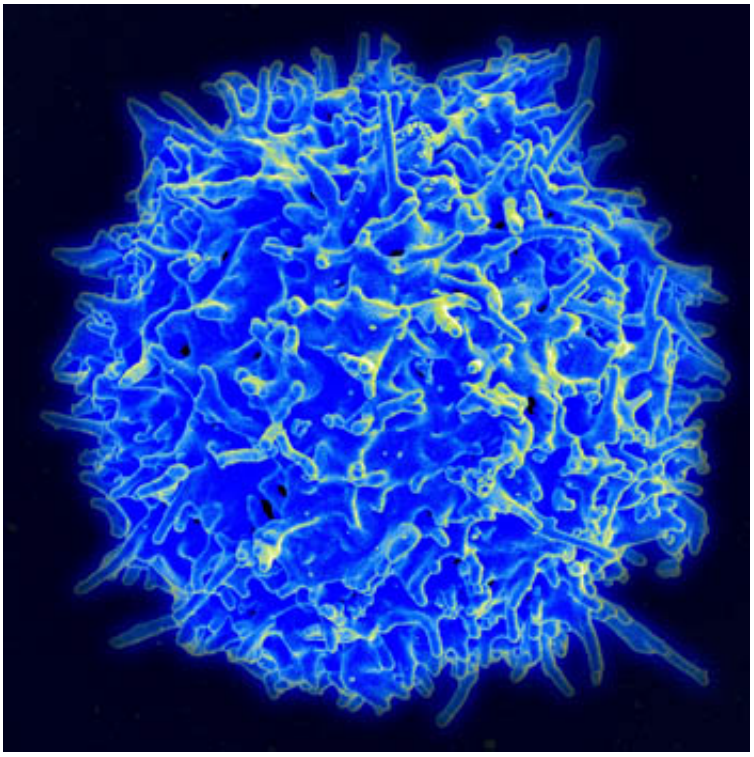

Scanning electron micrograph of human T lymphocyte or T cell. Credit: NIAID/NIH

Scientists have revealed for the first time how immature mouse immune cells, called T cells, choose which type of skills they will develop to fight malaria infection. Reported today in *Science Immunology*, researchers from the Wellcome Trust Sanger Institute, European Bioinformatics Institute and QIMR Berghofer Medical Research Institute, Australia,

tracked individual T cells during infection with malaria parasites. They discovered a whole network of chemical conversations between different types of cells that influenced T cell specialisation.

Using the latest single-cell genomics technology and computational modelling, the study also discovered genes within the T cells that may be involved in controlling antibody production during malaria infection. One of these, Galectin 1, encouraged development of a particular type of T cell when active. These genes are possible drug targets to boost immunity to malaria and other infections.

The immune system is extremely complex and responds to disease by developing specific types of immune cells. Two different types of T cell - T helper1 (Th1) and T follicular helper (Tfh) - develop and help fight infection. The researchers discovered that more Th1 cells were produced when a gene called Galectin 1 was active. These Th1 cells help remove parasites from the bloodstream and are needed early on in an infection, however for longer-term immunity, more Tfh cells are needed.

Dr Ashraful Haque, joint lead author from the QIMR Berghofer Medical Research Institute, Brisbane, Australia, said: "This is the first time that Galectin 1 acting inside T cells has been seen to influence Th1 fate, and has shown that Galectin 1 is a possible therapeutic target for malaria. An important next step will be to test many of the new gene targets identified by our studies, to see if they can be targeted by drugs to boost immunity to malaria."

The exact molecules that encourage the T cells to develop into one or the other form are poorly understood. The researchers used single-cell RNA sequencing to take 'snapshots' of the active genes produced by each individual T cell after the mouse was infected with malaria. With these snapshots of data, the researchers identified all the different stages between immature T cells and fully specialised Th1 or Tfh cells.

Dr Sarah Teichmann, Head of Cellular Genetics at the Sanger Institute and joint lead author on the paper, said: "This is the first high resolution time-course of cells using a pathogen in mice, where we have used cutting edge genomics coupled with computational methods to reconstruct how cells evolve and develop over infection. With methods from machine learning, we have simplified really complex biological processes into something we can understand. This approach could be applied to resolve any biological developmental process."

The team also developed a new computer modelling system called GPfates which allowed them to see how all the cells related to each other. This uses methods from spatio-temporal statistics, to show which genes were switched on in each of the two distinct cell states (Th1 and Tfh).

Dr Oliver Stegle, joint lead author from the European Bioinformatics Institute, said: "Using genomics we uncovered the inter-cellular conversation that is taking place between immune cells such as monocytes and Th1 cells. This has not been seen before, and our data have allowed us to uncover tens or hundreds of new genes that may be involved in controlling the production of antibodies. Activity in these genes may help the body, for example in curing an infection, or may hinder by allowing cancerous cells to flourish. The principles and the computational methods we have developed here could be applied to future studies to explore these questions."

More information: "Single-cell RNA-seq and computational analysis using temporal mixture modelling resolves TH1/TFH fate bifurcation in malaria," *Science Immunology*, immunology.sciencemag.org/look … 6/sciimmunol.aal2192

GPfates and a database, www.PlasmoTH.org, which facilitates discovery of novel factors controlling TH1/TFH fate commitment are available for

other scientists to use.

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