MedicalXpress

Novel genomic tools provide new insight into human immune system

January 19 2018

When the body is under attack from pathogens, the immune system marshals a diverse collection of immune cells to work together in a tightly orchestrated process and defend the host against the intruders. For many decades, immunologists sorted these cells into ever growing numbers of different types and subtypes mainly based on their morphology and phenotype to understand their function. But novel genomic tools are beginning to reveal new, rare cell types as well as unexpected variability and plasticity within groups upending the traditional view of immune cells assigned to the same category as unvarying entities that behave in a constant manner.

In their latest study, researchers at La Jolla Institute for Allergy and Immunology (LJI) used single-cell transcriptome analysis to identify a hitherto unknown precursor for a poorly understood subgroup of killer T cells that is primarily found in humans with chronic viral infections. Their detailed analysis of the entirety of transcribed genes in more than 9,000 individual cells also revealed an unprecedented level of heterogeneity.

The findings, published in the January 19, 2018, online edition of *Science Immunology*, provide new insights into how so-called CD4 cytotoxic T cells arise in humans and thus could facilitate improved vaccine design to protect against chronic viral infections such as cytomegalovirus, HIV, and hepatitis C.

"Continually evolving genomic tools and single cell analysis technologies

are revolutionizing our understanding of the human immune system in health and disease," says Pandurangan Vijayanand, M.D., Ph.D., Associate Professor and William K. Bowes Jr. Distinguished Professor at LJI who led the study. "But this is just the beginning of the genomic journey. By applying these tools in relevant diseases and cell types we are changing our understanding of the biology of human immune cells."

Based on cell surface markers known as CD4 and CD8, T cells generally fall into two broad categories: CD4-positive helper T cells, which¬ help activate other immune cells and CD8-positive cytotoxic T cells, which kill cells that are cancerous or infected with viruses. Under certain circumstances, however, a portion of helper T cells turns into cytotoxic T cells (CD4-CTLs). CD4 CTLs were originally reported in humans with chronic viral infections such as human cytomegalovirus (CMV), HIV, dengue virus and hepatitis C virus but have also been linked to protective antitumor immune responses, especially in virally induced tumors.

"The observed increase in the ratio of cytotoxic CD4 T cells to CD4 helper T cells indicates that they are an important component of the protective immune response to viral infections and that their induction should be an important marker for successful vaccinations against certain viral diseases," says postdoctoral researcher and first author Veena Patil, Ph.D. "But we really didn't know enough about their molecular profile and the mechanisms that drive their differentiation and maintenance."

To learn more, Patil analyzed thousands of individual CD4-CTLs isolated from peripheral blood from donors using single cell RNA sequencing, which can define different cell types and subtypes by revealing differences in the transcripts produced by individual cells. Her analysis uncovered remarkable heterogeneity between individual cells but also within individuals. "It is probably the result of the diverse nature of infections and timing of viral exposures coupled with genetic diversity

among our study subjects," she says.

Vijayanand and his team were also able to identify a subset of CD4-CTLs precursors that potentially give rise to fully fledged CD4 CTLs in human. "Understanding the origins and biology of potentially long-lived CD4-CTL precursors may pave the way for developing strategies to boost durable CD4-CTL immune responses after vaccination against viral infections and cancer," the authors write in their paper.

More information: Veena S. Patil, Ariel Madrigal, Benjamin J. Schmiedel, James Clarke, Patrick O'Rourke, Aruna D. de Silva, Eva Harris, Bjoern Peters, Gregory Seumois, Daniela Weiskopf, Alessandro Sette, Pandurangan Vijayanand. Precursors of human CD4+ cytotoxic T lymphocytes identified by single-cell transcriptome analysis. *Science Immunology*, 2018. DOI: 10.1126/sciimmunol.aan8664

Provided by La Jolla Institute for Allergy and Immunology