Cellular culprit suspected of pushing dengue fever from bad to worse is cleared by transcripts

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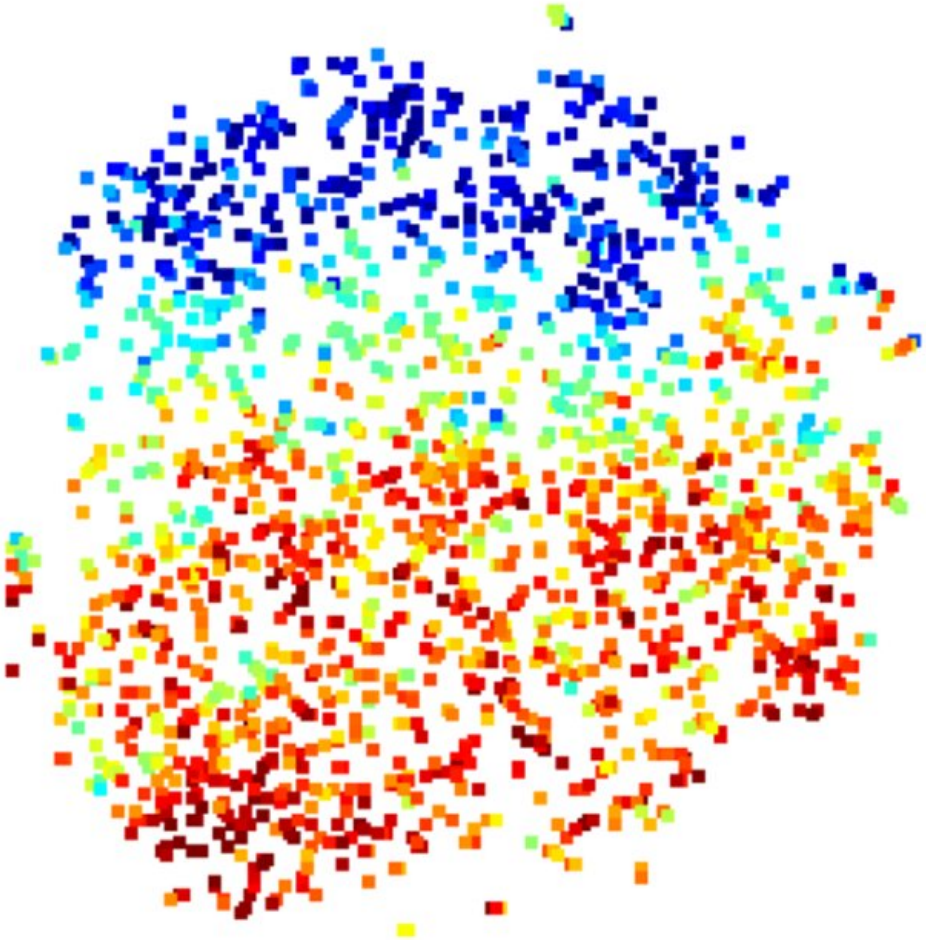

Dengue-specific CD4 cells have both a pro-inflammatory function and an anti-inflammatory function, which is typically not seen in acute viral infections. Each dot is a double positive cell with the color of each dot representing the expression level of a protein named TIGIT, which is an inhibitory immunoreceptor, in each cell. Credit: Dr. Yuan Tian, La Jolla Institute for Immunology

No one knows what makes a mild dengue viral infection morph into a severe and sometimes deadly dengue hemorrhagic fever/dengue shock syndrome. Experts previously believed the likely cause was ramped up activity of T cells, which can massively boost an immune response to a virus. Now, however, researchers at the La Jolla Institute for Immunology (LJI), have found definitive evidence that CD4 T cells, one of two main subtypes of T cells, are not to blame.

The finding, reported in the December 24, 2019, issue of *Cell Reports*, is important to both the basic understanding of this disease—the world's most common mosquito-borne illness—and to the hunt for an effective vaccine for dengue.

"We found no evidence to support the common dogma that these T cells are responsible for turning a mild infection to a severe one. This will help us narrow the search for the true culprit," says the study's lead investigator Yuan Tian, Ph.D., an AAI Intersect Fellow and a Bioinformatics Student at LJI. He is also a postdoctoral fellow in the lab of Alessandro Sette, Dr. Sci. Biol, a co-author of the study.

These issues are serious. Dengue fever is spreading. Infected mosquitos have expanded beyond their established tropical and subtropical

territories in South East Asia and Latin America to new continents, including Europe and the United States. More than half of the world's population is now at risk; already, 390 million infections occur annually, according to public health experts.

The goal of the LJI study was to define the molecular pattern of dengue-specific CD4 T cells and to investigate whether there is a difference in the T cell response between patients with mild dengue fever or with severe dengue hemorrhagic fever.

When analyzing dengue-specific CD4 T cells, the researchers realized that the responding CD4 T cells, have both a pro-inflammatory function (regulated by the cytokine interferon gamma, or IFN-γ) and an anti-inflammatory function (regulated by the cytokine interleukin 10, or IL-10) which is typically not seen in acute viral infections. To comprehensively define these dengue-virus specific T cells in hospitalized patients, researchers used whole transcriptome analysis to determine if there was a difference in the quality of the increased response.

This approach allows to identify all RNA transcripts—produced when a gene's DNA sequence is copied, or transcribed—within the transcriptome of dengue-specific CD4 T cells in hospitalized patients being treated for either mild or for severe dengue infection. These patients were being treated in Sri Lanka, where dengue fever is endemic.

"This is a very powerful approach to detect gene expression activity because all genes upregulated in response to the virus can be identified. It is completely unbiased and does not rely on pre-selected genes," says the study's senior investigator, Daniela Weiskopf, Ph.D., an instructor at LJI.

The research team, to their surprise, detected no difference in the

genomic profile of dengue-virus specific CD4 T cells regardless if they isolated them form patients with mild or severe dengue infection.

"The CD4 T cell response in the severe disease does not look different so that cannot be the switch we are all looking for," Tian says. "In fact, based on some intriguing preliminary findings, we speculate that to counteract the severe immune response occurring in acute cases, these dengue-specific CD4 cells may have gradually acquired the ability to produce more IL-10 by converting IFN-γ. It is as if they are trying to calm themselves, calm the inflammation. The double positive CD4 T cells could actually be helping, rather than hurting."

Tian adds that he hopes these findings will serve to "help guide efforts to develop effective dengue vaccines by improving our understanding of this novel T cell response."

More information: Yuan Tian, Grégory Seumois, Luzia M. De-Oliveira-Pinto, Jose Mateus, Sara Herrera-de la Mata, Cheryl Kim, Denise Hinz, N.D. Suraj Goonawardhana, Aruna D. de Silva, Sunil Premawansa, Gayani Premawansa, Ananda Wijewickrama, Angel Balmaseda, Alba Grifoni, Pandurangan Vijayanand, Eva Harris, Bjoern Peters, Alessandro Sette, and Daniela Weiskopf. "Molecular Signatures of Dengue Virus-Specific IL-10/IFN-γ Co-producing CD4 T Cells and their Association with Dengue Disease." *Cell Reports*, 2019. DOI: 10.1016/j.celrep.2019.11.098

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