In First Moments of Infection, a Division and a Decision

UC San Diego scientists explain how and when T cells become effector or memory lymphocytes

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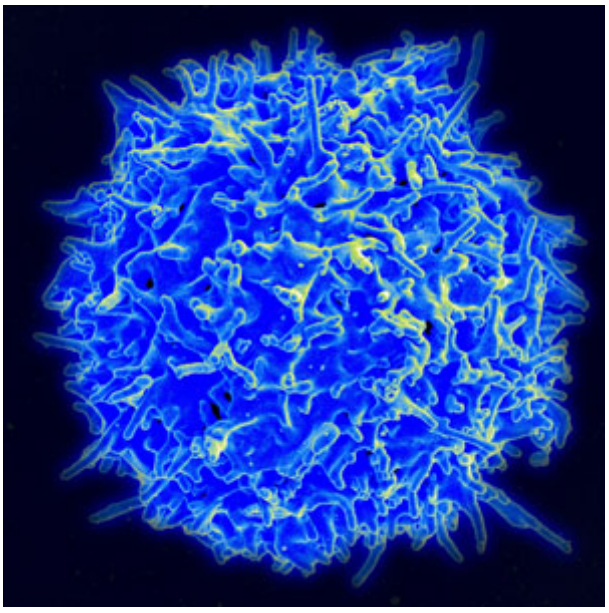
Using technologies and computational modeling that trace the destiny of single cells, researchers at the University of California, San Diego School of Medicine describe for the first time the earliest stages of fate determination among white blood cells called T lymphocytes, providing new insights that may help drug developers create more effective, longer-lasting vaccines against microbial pathogens or cancer.

The findings are published in the March 2, 2014 online issue of *Nature Immunology.*



T lymphocyte. Image courtesy of the National Institute of Allergy and Infectious Diseases.

Naïve T lymphocytes patrol the front lines of the human body's defense against infection, circulating in blood and tissues, searching for invasive microbes and other foreign antigens. They're called "naïve" because they have not yet encountered an invader. When they do, these T cells activate and divide, giving rise to two types of daughter cells: "effector lymphocytes" responsible for immediate host defense and "memory lymphocytes" that provide long-term protection from similar infections.

"Researchers have been trying for a very long time to understand when and how T lymphocytes give rise to effector and memory cells during an infection," said John T. Chang, MD, assistant professor in the Department of Medicine and the study's co-principal investigator, along with Gene W. Yeo, PhD, assistant professor in the Department of Cellular and Molecular Medicine and Institute for Genomic Medicine.

However, all studies up to this point were based on analyses on bulk populations of cells, making it impossible to understand fate decisions made by individual cells. First authors Janilyn Arsenio, a

postdoctoral fellow in the Chang lab and Boyko Kakaradov, a graduate student in the Yeo lab and UCSD Bioinformatics graduate program said that they took advantage of recent technological advances in single-cell gene expression profiling and cutting-edge machine-learning algorithms to address this question on a level of detail that was not previously possible.

Chang, Yeo and colleagues discovered that the decision by an individual T cell to produce effector and memory cells is made almost at the moment of infection. "The 'mother' lymphocyte seems to divide into two daughter cells that are already different from birth," said Chang, "with one becoming an effector cell while its sister becomes a memory cell."

Chang noted that the primary purpose of vaccines is to produce strong and durable immune protection, which depends heavily upon generation of memory lymphocytes. "Our work suggests that the way T lymphocytes divide early during a microbial infection might be critical to whether or not they give rise to long-lived memory cells. Strategies that improve this process could potentially enhance durable immunity and help us to design more effective vaccines."

Co-authors of the study include Janilyn Arsenio, Patrick J. Metz and Stephanie H. Kim, UCSD Department of Medicine; Boyko Kakaradov, UCSD Department of Cellular and Molecular Medicine, UCSD Stem Cell and Bioinformatics programs and Institute for Genomic Medicine, UCSD; and Gene W. Yeo, UCSD Department of Cellular and Molecular Medicine, UCSD Stem Cell and Bioinformatics programs and Institute for Genomic Medicine, UCSD and National University of Singapore and Genome Institute of Singapore.

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