Team identifies important regulators of immune cell response

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In a collaborative study, scientists from the Florida campus of The Scripps Research Institute (TSRI) and the La Jolla Institute for Allergy and Immunology have developed a more effective method to determine how immune cells called T cells differentiate into specialized types of cells that help eradicate infected cells and assist other immune cells during infection.

The new approach, published recently by the journal *Immunity*, could help accelerate laboratory research and the development of potential therapeutics, including vaccines. The method may also be used to identify the genes that underlie tumor cell development.

There are approximately 40,000 genes in each of our cells, but functions for only about half of them are known. The classical approach to determine the function of individual genes is slow.

"Typically, studies to identify differentiation players are done one gene at a time," said Associate Professor Matthew Pipkin of TSRI, who led the study with Professor Shane Crotty of the La Jolla Institute for Allergy and Immunology. "Our study describes a novel method that can 'screen' entire gene families to discover the functions of a large number of individual genes simultaneously, a far more efficient methodology."

In the new study, the team examined genes that regulate the specialization of T cells into "effector" cells that eliminate pathogens during infection and "memory" cells that survive long-term to maintain

guard after the first infection has been cleared, keeping the same pathogens from re-infecting the body after it has fought them off once.

In their experiments, Pipkin, Crotty and their colleagues created a mixture of T cells, identical except that the expression of a different gene was interrupted in each cell so the pool of cells represented disruption of a large set of genes. The researchers then assessed the cells' response to lymphocytic choriomeningitis virus (LCMV). Before-and-after-infection studies revealed which cells with interrupted genes had emerged after infection; cells in which disruption of a particular gene resulted in it being lost from the mixture indicated the gene played a role in promoting the cell's development into an antiviral T cell.

The study successfully identified two previously unknown factors that work together during T cell differentiation—Cyclin T1 and its catalytic partner Cdk9, which together form the transcription elongation factor (P-TEFb). While widely expressed throughout the body and used in a number of developmental processes, the factors were previously unknown to be important in the differentiation of both antiviral CD4 and CD8 T cells.

"One of the regulators we uncovered normally enhances effector T cell differentiation at the expense of generating memory T cells and T cells that orchestrate antibody production," Pipkin said. "That's one candidate that you'd want to 'turn down' if you wanted to create more T cells that form memory cells and promote a more effective antibody response—something that would be extremely helpful in developing a vaccine."

More information: "In Vivo RNA Interference Screens Identify Regulators of Antiviral CD4+ and CD8+ T Cell Differentiation," www.cell.com/immunity/abstract … 1074-7613(14)00272-6

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