Researchers determine how inflammatory cells function, setting stage for future remedies

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A research team led by investigators at New York University and NYU School of Medicine has determined how cells that cause inflammatory ailments, such as Crohn's disease, multiple sclerosis, and arthritis, differentiate from stem cells and ultimately affect the clinical outcome of these diseases.

"We've found that hundreds of new genes are involved in the function and development of these cells," said co-author Richard Bonneau, an associate professor at New York University's Center for Genomics and Systems Biology and the Courant Institute of Mathematical Sciences. "This expansion in our understanding can be used as a framework for designing new therapies to combat a range of ailments where the immune system attacks self."

These cells, called T-cells by immunologists, play a role in fighting off infection, but can also induce inflammation and other processes that damage tissues and contribute to several common inflammatory diseases. T-cells are also key cell types in new immune-cell based therapies for fighting cancer. There are many types of T-cells, and how they differentiate from stem cells in the human body lies at the center of understanding several diseases.

"We have been striving for several years to understand what makes inflammatory T-lymphocytes special," said lead investigator Dan

Littman, MD, PhD, the Helen L. and Martin S. Kimmel Professor of Molecular Immunology and a professor of pathology, microbiology and molecular pathogenesis at NYU School of Medicine and a faculty member of the Skirball Institute on Biomolecular Medicine. "They can protect us from microbes, but they also have the potential to cause autoimmune disease.

"We were fortunate to be able to bring together a team of immunologists, computational biologists, and genomics experts to begin to solve this puzzle. Whereas before we only knew of a handful of genes that influence the function of these cells, we now know of hundreds of new ones that can serve as a resource for further studies by us and other laboratories. Our hope is that some of these new molecules will be the Achilles heel that we can target to treat these diseases."

The findings, which are reported in the latest issue of the journal *Cell*, lay the groundwork for understanding how these cells regulate their genomes through a regulatory network that connects many environmental stimuli to a large number of genes and their interactions. This large network model is essentially the brain that T-cell precursors, or stem cells, use to decide what they want to be when they grow up. Specifically, a network model can be used simulate what inhibiting a gene with a drug would do to different T-cells and, in this way, aid the development of new therapeutic measures to address these afflictions.

The study focused on T-helper 17 cells (Th17) and how they regulate the synthesis of gene products from thousands of regions of the chromosome. Th17 cells have previously been implicated in inflammatory diseases. Other studies have also identified hundreds of genes that roles in pro-inflammatory diseases. This new study places these implicated genes on a timeline of cellular development and ultimately puts them together in an integrated model of how genes interact.

To explore the inner workings of these cells, the researchers used a systems biology approach, which focuses measuring multiple biomolecules and capturing multiple interactions within an organism to understand how it functions. For example, each of the 450 data sets integrated in this study contained measurements of gene expression, chromatin structure, or gene-chromosome interaction that spanned millions of locations along the genome. This holistic method offers a broader understanding of interconnected molecular phenomena essential to running life's program—a process similar to studying an entire automobile while it functions rather than separately studying the headlights, brakes, or steering column.

To extract meaningful results from this very large data set, the researchers employed statistical techniques to uncover the network model from the large amount of data. To verify the accuracy of the computer modeling, further laboratory experiments were conducted using mice. Although the study was carried out in mice, the researchers found that their work could offer explanations as to why a large number of genes are associated with several human inflammatory diseases. The researchers' computer models identified candidate genes that influence the expression of more than 2,000 genes and play a significant role in the regulation of Th17 cells. They found that the core of this network was significantly enriched for the genes that human geneticists have found to be associated with pro-inflammatory disease. These genes serve as cogs in the regulation of expression or suppression of genes in Th17 cells and are potential leads for developing new therapeutic approaches to modulating inflammation.

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