When it comes to the immune system, we're all more alike than previously thought, study finds

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When it comes to the mechanics of the human immune system, we are all more alike than previously thought, according to a new study by scientists at Fred Hutchinson Cancer Research Center.

This finding has significant implications for developing new ways to detect, diagnose and treat cancer and diseases of the immune system, according to Harlan Robins, Ph.D., corresponding author of a paper detailing the research in the Sept. 1 issue of Science Translational Medicine.

Robins and colleagues developed a novel way to sequence millions of T-cell receptors, a critical component of the human adaptive immune system, simultaneously from a single sample. When comparing immune system profiles from different people, the researchers were surprised to find that we are all more alike than previously thought.

"We found that any two people may share tens of thousands of the exact same T-cell receptor. This is contrary to previous dogma that each person has a distinct set of T-cell receptors with little or no overlap between people," said Robins, Ph.D., a computational biologist and an assistant member of the Public Health Sciences Division at the Hutchinson Center.

The findings have diagnostic and therapeutic potential for autoimmune

diseases and cancer.

"The strong similarity in the adaptive immune cells between different people suggests that the same disease will induce the same response in different people," Robins said. "The technology described in this paper can readily detect such a response, even if the magnitude of the immune reaction is small. Therefore, we potentially could use one or more of these shared T-cell responses as a diagnostic for a particular disease."

The part of the human immune system responsible for protection against novel pathogens, called the adaptive immune system, is composed of tens of millions of different subtypes of cells. Each cell subtype expresses a different receptor on its surface. These receptors are proteins, each of which has a unique shape so that together they can bind to a wide range of differently shaped pathogens. The set of receptors the researchers analyzed are called T-cell receptors, which develop in the thymus. Unlike the rest of the genes in the human genome, the genes that code for these T-cell receptors are not inherited; they develop separately in each person. The huge quantity and variety of T-cells in each person has prevented in-depth study - until now.

For the study, Robins and colleagues in the Hutchinson Center's Clinical Research Division sequenced more than five million T-cell receptor DNA strands from each of seven healthy donors. After comparing these sequences, they found two primary results.

First, the set of T-cell receptor sequences used by the human immune system is not a random cross section of all the possibilities, but a small subset with consistent properties that the scientists subsequently identified.

"Each person's adaptive immune system is far more alike than expected," Robins said.

Second, pair-wise comparisons of the T-cell receptors in the seven donors revealed that that tens of thousands of identical receptors are shared by each pair, even in people of different ethnicities.

This discovery has particular implications for autoimmune diseases and cancers, Robins said. For certain autoimmune diseases, such as Type 1 diabetes and multiple sclerosis, T-cells themselves are believed to play a causative role because they attack the body's cells. In Type 1 diabetes the adaptive immune system attacks the pancreatic islet cells, and for MS the immune system targets the cells that form the myelin sheaths around neurons in the brain and spinal cord. Most autoimmune diseases are diagnosed only after significant disease progression. However, by this time, irreparable cell damage has occurred.

"The results of our paper suggest that a specific set of T-cells that we can now detect are likely to play a causative role in the disease," Robins said. "Further, we can detect this targeted set much earlier than present diagnostics, perhaps saving vital cell function with the preventive administration of currently available therapeutics. And, because the T-cell clones are causative of the disease, they also double as therapeutic targets. In principle, a monoclonal antibody could be developed to target these T-cell clones and prevent the autoimmune attack."

The findings also present a potential new direction for cancer biomarkers to detect the disease early, while it is still curable. For many cancers, such as colon cancer, there is compelling evidence that a T-cell immune response is induced. The immune system operates through a process called clonal expansion. The set of T cells with specific receptors that bind to the infected cell make millions of copies of themselves to create an army to fight the full set of infected cells.

"Effectively, the immune system is an amplifier. So a very small tumor has the potential to induce a magnified immune response," Robins said.

"We are readily able to detect such a response. The results of this paper suggest that multiple patients might have a similar response to the same type of tumor. Therefore, detection of these similar responses could be an early diagnostic for certain types of cancer."

The scientists developed sequencing technology called ImmunoSEQ and associated software called the ImmunoSEQ Analyzer to process and analyze the immense amount of data that the experiments produced. The Hutchinson Center has patents pending on the sequencing technologies, which have been licensed exclusively to Adaptive TCR Corporation, a local company offering the sequencing and analysis services commercially.

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