Rare disorder gives modelers first glimpse at immune system development

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Children born without thymus glands have given Duke University Medical Center researchers a rare opportunity to watch as a new immune system develops its population of infection-fighting T-cells.

Researchers led by Thomas Kepler, Ph.D., Division Chief of Computational Biology, tracked three young patients after thymus tissue transplantation to measure the growth of a T cell population - with all of its diversity. Duke University pioneered thymus transplantation for children born with DiGeorge Syndrome, lacking a thymus, under the direction of Louise Markert, M.D., Ph.D.

As transplanted thymus tissue took hold in the children, the team studied signals related to specific T-cell receptors and more general resources like cytokine signals or space availability. They assessed T cell receptor diversity to determine overall T cell levels and to count T cells of certain kinds.

"What we haven't understood until now is how maintaining the diversity of T cells with different receptors works while a body also maintains appropriate T cell numbers overall," said Kepler, who is senior author of a paper published in *PloS Computational Biology*. "Our paper is the first to use information about changes in T cell receptor diversity to infer properties of the T cell regulatory mechanisms."

The immune system needs a variety of different T cells to fight all kinds of pathogens. "The fastest way to grow the total T cell population is to

impede diversity and grow just a few kinds of T cells," Kepler said. "We set out to understand more about the regulation of this fine balance."

Kepler and lead author Stanca Ciupe, Ph.D., a postdoctoral fellow in computational immunology, created mathematical formulas to model the contribution of resources on the regulation of T cell population growth and diversity. They found that factors that are blind to T cell receptors and treat all T cells alike are a thousand times more common than the factors that regulate receptor-specific development of T cells.

"The findings open up the possibility of studying the development of T cells in children with DiGeorge syndrome in a rigorous and quantifiable way, because we can determine which factors are most important," said Markert, a Duke Associate Professor of Pediatrics in the Division of Allergy and Immunology.

For example, one of the transplants appeared not to be functioning, based on a biopsy. Using the computations devised for this research, however, the team was able to track the rise in certain types of T cells - the transplant took longer to develop T cells than most other cases. In the end, the child's immune system matured, T cells developed, and the child avoided undergoing a second transplantation.

"What is novel is our ability to take the results from assays and quantify them to get a numerical measure of diversity, to get a picture of what really happens when T cells mature," Ciupe said. "Secondly, we were able to develop a mathematical model to feed the data into."

"It will require a significant mathematical effort to see the full promise of human systems biology come to fruition," Kepler said. "So much scientific work is done in model organisms, but we can't manipulate humans in those ways. This paper shows that with more sophisticated mathematical tools, you can get the information you need to learn about

human biology without enormous amounts of manipulation of people."

Ciupe said that using applying mathematics to biological systems and biological engineering will continue to develop new applications for humans. Mathematics might help to deliberately design human vaccines, for instance. "Physics and mathematics have a symbiotic relationship and resulted in the laws of physics," she said. "Combining biology and math is an iterative process, and someday we may have laws of biology in the same way."

Source: Duke University Medical Center (news : web)