MedicalXpress

Scientists develop computer models simulating stem cell transplant recovery

March 17 2016

Scientists at Virginia Commonwealth University have developed computer models that can simulate the recovery of the immune system in patients undergoing stem cell transplants. In two recent studies, they reinforce the potential of using DNA sequencing and computer modeling to predict which stem cell transplant recipients might suffer complications such as graft-versus-host-disease, a condition where the donor's immune system attacks the recipient's body. The studies build upon prior research by scientists at VCU Massey Cancer Center, the VCU Center for the Study of Biological Complexity and VCU's Department of Psychiatry and Statistical Genomics that found evidence that the immune system may be modeled as a dynamical system.

Dynamical systems describe phenomenon in which the relationships between the variables in the system determine its future state. Some systems, such as a swinging pendulum on a clock, can have relatively few variables, making their future states fairly easy to predict. Other systems, such as the weather, require advanced forecasting models due to the large number of variables affecting their present and future conditions. The ability to "forecast" immune system recovery could potentially allow doctors to better personalize post-transplant care for improved patient outcomes.

The first study, published in the journal *Biology of Blood and Marrow Transplantation*, sequenced the DNA of 34 stem cell transplant donor-recipient pairs and used the resulting information in an advanced computer model to simulate how the recipient's T cell repertoire will

recover following transplantation. The T cell repertoire is the army of immune system cells called T cells that a person develops in response to disease and other pathogens in their environment.

"This study is the first to simulate the growth of the T cell repertoire following transplantation using variables that aren't accounted for in typical HLA donor-recipient matching," says Amir Ahmed Toor, M.D., hematologist-oncologist in the Bone Marrow Transplantation Program and member of the Developmental Therapeutics research program at VCU Massey Cancer Center as well as associate professor in the Division of Hematology, Oncology and Palliative Care at the VCU School of Medicine. "Using a larger cohort of patients than in previous studies, we were able to mathematically predict the interactions of these variables, which led to simulations that appear to be very similar to clinically observed post-transplantation T cell repertoire development."

Human leucocyte antigen (HLA) testing is the current gold standard for matching stem cell transplant (SCT) donors and recipients. The HLA is a system of genes responsible for regulating immune responses. However, previous research by Toor and his colleagues uncovered large variations between donor-recipient minor histocompatibility antigens (mHA) that could potentially contribute to transplant complications not accounted for by HLA testing. mHA are protein fragments presented on the surface of the molecules that the HLA creates in order to regulate immune responses.

The models used in the computer simulations were driven by population growth formulas developed from past studies by Toor that discovered distinct patterns of lymphocyte recovery in SCT recipients. Using matrix mathematics to develop the simulations, the researchers also observed competition among T cells as the T cell repertoire develops. This competition leads to certain families of T cells becoming dominant and more numerous, which crowds out weaker T cell families, causing them

to develop later and in fewer numbers.

"We are attempting to account for the many variables that could impact T cell repertoire development and, in turn, patient outcomes," says Toor. "In future studies, we hope to explore the impact of organ-specific antigen expression. The knowledge gained from this research could potentially allow more accurate predictions of which organs could be most affected by graft-versus-host-disease."

The second study, published in the *Journal of the Royal Society Interface*, examines the ordering of the DNA segments that make up the T cell receptor loci, which are the part of the genome responsible for assembling the T cell repertoire. In this study, he provides further evidence of an underlying mathematical order and presents trigonometric ratios describing the positioning of the DNA segments.

Toor also hypothesizes that interactions between the two strands in the DNA double helix may influence gene segment order based on wave-mechanical properties inherent to the structure of DNA. If true, this theory has implications for understanding the entire genome as it could allow scientists to quantify gene expression.

"Typically, the locations of gene segments are considered as if they were numbers on a straight line," says Toor. "This study is unique in that we have used trigonometry to account for the spiral nature of DNA."

Toor's research is an exciting marriage of nature, math and science applied for human health. If successful, it could lead not only to improved stem cell transplantation practices but also a much greater understanding of how our body assembles the building blocks needed to keep us alive.

More information: The full manuscript for the *Biology of Blood and*