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LINEAGE TREES FOR CELLS

Some fundamental outstanding questions in science: “Where do stem cells originate?” “How does cancer develop?” “When do cell types split off from each other in the embryo?” might be answered if scientists had a way to map the history of the body’s cells going back to the fertilized egg. Now, a multidisciplinary team at the Weizmann Institute of Science has developed an analytical method that can trace the lineage trees of cells.

This accomplishment started with a challenge to common wisdom, which says that every cell in an organism carries an exact duplicate of its genome. Although mistakes in copying, which are passed on to the next generation of cells as mutations, occur when cells divide, such tiny flaws in the genome are thought to be trivial and mainly irrelevant. But research students Dan Frumkin, and Adam Wasserstrom of the Biological Chemistry Department, working under the guidance of Prof. Ehud Shapiro of the Institute’s Biological Chemistry, and Computer Science and Applied Mathematics Departments, raised a new possibility: Though biologically insignificant, the accumulated mutations might hold a record of the history of cell divisions.

Together with Prof. Uriel Feige, of the Computer Science and Applied Mathematics Department, and research student Shai Kaplan, they proved that these mutations can be treated as information and used to trace lineage on a large scale, and then applied the theory to extracting data and drafting lineage trees for living cells.

Methods employed until now for charting cell lineage trees have relied on direct observation of developing embryos. This method worked well enough for the tiny, transparent worm, *C. elegans*, that has around 1000 cells, all told, but for humans, with 100 trillion cells, or even newborn mice or human embryos at one month, each of which has a billion cells after some 40 rounds of cell division, the task would be impossible.

The study focused on mutations in specific, mutation-prone areas of the genome known as microsatellites. In microsatellites, a genetic “phrase” consisting of a few nucleotides (genetic “letters”) is repeated over and over; mutations manifest themselves as additions or subtractions in length. Based on the current understanding of the mutation process in these segments, the scientists proved mathematically that microsatellites alone contain enough information to accurately plot the lineage tree for a one-billion-cell organism.

Both human and mouse genomes contain around 1.5 million microsatellites, but the team's findings demonstrated that a useful analysis can be performed based on a much smaller number. To obtain a consistent mutation record, the team used organisms with a rare genetic defect found in plants and animals alike. While healthy cells have repair mechanisms to correct copying mistakes and prevent mutation, cells with the defect lack this ability, allowing mutations to accumulate relatively rapidly.

Borrowing a computer algorithm used by evolutionary biologists that analyzes genetic information in order to place organisms on branches of the evolutionary tree, the researchers assembled an automated system that samples the genetic material from a number of cells, compares it for specific mutations, applies the algorithm to assess degrees of relatedness and from there outlines the cell lineage tree. To check their system, they pitted it against the tried and true method of observing cell divisions as they occurred in a lab-grown cell culture. The team found that, from an analysis of just 50 microsatellites, they could successfully recreate an accurate cell lineage tree.

While the research team plans to continue to test their system on more complex organisms such as mice, several scientists have already expressed interest in integrating the method into ongoing research in their fields. Says Shapiro, who heads the project: "Our discovery may point the way to a future "Human Cell Lineage Project" that would aim to resolve fundamental open questions in biology and medicine by reconstructing ever larger portions of the human cell lineage tree."

For additional information see

www.weizmann.ac.il/udi/plos2005 <<http://www.weizmann.ac.il/udi/plos2005>>.

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The Weizmann Institute of Science in Rehovot, Israel, is one of the world's top-ranking multidisciplinary research institutions. Noted for its wide-ranging exploration of the natural and exact sciences, the Institute is home to 2,500 scientists, students, technicians and supporting staff. Institute research efforts include the search for new ways of fighting disease and hunger, examining leading questions in mathematics and computer science, probing the physics of matter and the universe, creating novel materials and developing new strategies for protecting the environment.

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