Medical Xpress

Researchers connect new genetic signature to leukemia

August 27 2012

(Medical Xpress)—University of Rochester Medical Center scientists believe they are the first to identify genes that underlie the growth of primitive leukemia stem cell, and then to use the new genetic signature to identify currently available drugs that selectively target the rogue cells.

Although it is too early to attach significance to the drug candidates, two possible matches popped up: A drug in development for breast cancer (not approved by the Food and Drug Administration), and another experimental agent that, coincidentally, had been identified earlier by a URMC laboratory as an agent that targets leukemia cells.

The research not only provides a better understanding of the basic biology of leukemia—it uncovered genes not previously known to be associated with the disease—but demonstrates a powerful strategy for drug discovery, said senior investigator Craig T. Jordan, Ph.D., the Philip and Marilyn Wehrheim professor of Medicine at URMC and the James P. Wilmot Cancer Center.

First author John Ashton, PhD, led the study, which was published this month in the journal *Cell Stem Cell*.

"Our work is both basic and translational, and is an example of a terrific collaboration," Jordan said. "We were able to use the latest technology to expand very strong basic laboratory concepts and conduct an intriguing analysis that may yield new insights for treatments of leukemia."

Jordan studies leukemia stem cells, which, unlike normal cells, renew uncontrollably and are believed to be the first cells at the root of malignancy. He collaborated with Harmut (Hucky) Land, Ph.D. and Helene McMurray, Ph.D., investigators in Biomedical Genetics at URMC, who study the principle that cancer evolves from a unique, interactive network of genes that are governed by a distinct set of rules.

In 2008 Land's laboratory published a paper in *Nature* reporting on a pool of approximately 100 genes that cooperate to promote colon cancer. The Land laboratory coined the term CRG for "cooperation response genes," to emphasize the special synergy controlling this pool of genes. Land is the Robert and Dorothy Markin Professor and Chair of the Department of Biomedical Genetics at URMC, and co-director of the Wilmot Cancer Center.

The identification of CRGs broadened the view of cancer, Jordan said. Historically, scientists would study the intricacies of one or two individual pathways in a vast network of alterations. With the advent of CRGs, however, researchers now have a better picture of the sub-populations of genes that dole out instructions to primitive cancer cells, like controls on a circuit board. Depending on whether CRGs are turned off or on, patterns change and cancer either progresses or stops, Land's research showed.

Leukemia is notoriously resistant to treatment, and thus it makes a good target for new therapies. Most relapses occur because modern therapies are not designed to attack at the biologically distinct stem-cell level and thus, residual cancer circulates in the bloodstream.

Using mouse models and human leukemia specimens, Jordan's team found approximately 70 CRGs that played a role in growth and survival of both primitive leukemia cells and more mature leukemia cells. Knocking out expression of the CRGs in mice reduced leukemia growth.

With the newly identified CRG signature for leukemia, researchers then employed the Broad Institute's Connectivity Map, a sophisticated genomics tool open to the public since 2007. CMAP catalogs hundreds of known drug compounds and allows researchers to search for drugs that mimic the genomic disease signatures.

Jordan's group wondered if any drugs in the database could suppress or reverse the function of the CRGs that control leukemia growth. They identified the best candidates, and those were tested further in the lab.

"No one else has used the targeting of CRGs as criteria to look for drugs that might treat cancer," Jordan said. "By using the CRG approach, we found drug compounds that might never have been selected, based on their documented mechanism of action."

Although the Connectivity Map database does not contain every available drug in the world, Jordan noted that it is periodically updated. Meanwhile, his lab is conducting parallel studies to validate the latest findings. (In related research, Jordan also discovered a plant-based compound that destroyed leukemia stem cells in lab experiments; that drug is now undergoing a Phase 1 clinical trial.)

More information: www.cell.com/cell-stem-cell/ab … 1934-5909(12)00351-7

Provided by University of Rochester Medical Center