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Researchers Block Pathway to Cancer Cell Replication

NOTCH1 Signaling Promotes T-Cell Acute Lymphoblastic Leukemia-Initiating Cell Regeneration

Research suggests that patients with leukemia sometimes relapse because standard chemotherapy fails to kill the self-renewing leukemia initiating cells, often referred to as cancer stem cells. In such cancers, the cells lie dormant for a time, only to later begin cloning, resulting in a return and metastasis of the disease.

One such type of cancer is called pediatric T cell acute lymphoblastic leukemia, or T-ALL, often found in children, who have few treatment options beyond chemotherapy.

A team of researchers – led by Catriona H. M. Jamieson, MD, PhD, associate professor of medicine at the University of California, San Diego School of Medicine and Director of Stem Cell Research at UC San Diego Moores Cancer Center – studied these cells in mouse models that had been transplanted with human leukemia cells. They discovered that the leukemia initiating cells which clone, or replicate, themselves most robustly activate the NOTCH1 pathway, usually in the context of a mutation. The results appear online in the journal *PLoS ONE*.

Earlier studies showed that as many as half of patients with T-ALL have mutations in the NOTCH1 pathway – an evolutionarily conserved developmental pathway used during differentiation of many cell and tissue types. The new study shows that when NOTCH1 activation was inhibited in animal models using a monoclonal antibody, the leukemia initiating cells did not survive. In addition, the antibody treatment significantly reduced a subset of these cancer stem cells (identified by the presence of specific markers, CD2 and CD7, on the cell surface.)

“We were able to substantially reduce the potential of these cancer stem cells to self-renew,” said Jamieson. “So we’re not just getting rid of cancerous cells: we’re getting to the root of their resistance to treatment – leukemic stem cells that lie dormant.”

The study results suggest that such therapy would also be effective in other types of cancer stem cells, such as those that cause breast cancer, that also rely on NOTCH1 for self-renewal.

“Therapies based on monoclonal antibodies that inhibit NOTCH 1 are much more selective than using gamma-secretase inhibitors, which also block other essential cellular functions in addition to the NOTCH1 signaling pathway,” said contributor A. Thomas Look, MD of Dana-Farber/Children Hospital Cancer Center in Boston. “We are excited about the promise of NOTCH1-specific antibodies to counter resistance to therapy in T-ALL and possibly additional types of cancer.”

In investigating the role of NOTCH1 activation in cancer cell cloning, the researchers showed that leukemia initiating cells possess enhanced survival and self-renewal potential in specific blood-cell, or hematopoietic, niches: the microenvironment of the body in which the cells live and self-renew.

The scientists studied the molecular characterization of CD34+ cells – a protein that shows expression in early hematopoietic cells and that facilitates cell migration – from a dozen T-ALL patient samples.

They found that mutations in NOTCH1 and other genes capable of promoting the survival of cancer stem cells co-existed in the CD34+ niche. Mice transplanted with CD34-enriched NOTCH1 mutated T-ALL cells demonstrated significantly greater leukemic cloning potential than did mice without the NOTCH1 mutation. The mutated cells were uniquely susceptible to targeted inhibition with a human monoclonal antibody, according to the scientists.

Additional contributors to the study include Wenxue Ma, Daniel J. Goff, Ifat Geron, Anil Sadarangani, Christina A. M. Jamieson, Angela C. Court, Alice Y. Shih, Qingfei Jiang, Christina C. Wu, Kristen M. Smith, Leslie A. Crews, Ida Deichaite, Sheldon R. Morris and Dennis A. Carson, UC San Diego Department of Medicine and Stem Cell Program, UC San Diego Moores Cancer Center; Alejandro Gutierrez, Dana-Farber/Children Hospital Cancer Center in Boston; and Kang Li, Ping Wei and Neil W. Gibson, Oncology Research Unit, Pfizer Global Research and Development, La Jolla Laboratories, San Diego.

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