Leukemic cells find safe haven in bone marrow

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The cancer drug asparaginase fails to help cure some children with acute lymphoblastic leukemia (ALL) because molecules released by certain cells in the bone marrow counteract the effect of that drug, according to investigators at St. Jude Children's Research Hospital.

The researchers showed that mesenchymal cells in the bone marrow create a protective niche for leukemic cells by releasing large amounts of asparagine, an amino acid that nearby leukemic cells must have to survive but do not make efficiently. This extra supply of asparagine helps leukemic cells survive treatment with asparaginase, a drug that normally would deplete their supply of this vital nutrient, the researchers reported. Mesenchymal cells give rise to a variety of different tissues, such as osteoblasts (bone-building cells) and chondrocytes (cartilage-building cells), and form the nurturing environment where normal blood cells and leukemic cells grow.

"Leukemic cells that resist asparaginase and survive in this protective niche of the bone marrow might be the reason that leukemia recurs in some children who have been treated with this drug," said Dario Campana, M.D., Ph.D., a member of the St. Jude Oncology and Pathology departments.

Campana is senior author of the report that appears in the online pre-publication issue of "The Journal of Clinical Investigation."

"Our findings indicate that the level of activity of the "ASNS" gene in

the mesenchymal cells is key to protecting leukemic cells in the bone marrow from asparaginase," Campana said. "This insight will help researchers find ways to disrupt this safe haven for leukemic cells that need asparagine," added James R. Downing, M.D., St. Jude scientific director and chair of the Pathology department. Downing is a co-author of "The Journal of Clinical Investigation" paper. The "ASNS" gene controls production of the enzyme asparagine synthetase (ASNS), which leukemic cells use to make asparagine.

The study's findings also suggest that drugs now being developed to block ASNS should be tested to see if they also prevent mesenchymal cells from making this amino acid. In addition, the ability of mesenchymal cells to make asparagine might be decreased by cancer drugs that are already known to disrupt the activity of those cells.

"Because asparaginase is so widely used to treat ALL, this new insight into how mesenchymal cells protect leukemic cells is very important," said Ching-Hon Pui, M.D., chair of the Oncology department and American Cancer Society Professor at St. Jude. "The more we learn about the molecular interactions between these cells, the more likely we'll be able to enhance the anti-leukemic action of asparaginase and perhaps other anti-leukemic drugs as well," said Pui, a co-author of the paper. "That would reduce the recurrence rate of ALL and continue our successful efforts to increase the survival rate of ALL."

Previous research at St. Jude and elsewhere had shown that direct contact with bone marrow mesenchymal cells is essential for the long-term survival and multiplication of leukemic lymphoblasts. In the current study, the team found that the gene for ASNS was more than 20 times active in producing this enzyme in mesenchymal cells than in ALL cells.

Experiments performed by co-authors Shotaro Iwamoto, M.D., and Keichiro Mihara, postdoctoral fellows in Campana's laboratory,

demonstrated that ALL cells from different patients became much more resistant to asparaginase when cultured on top of a layer of mesenchymal cells. In order to determine whether it was the high levels of asparagine released by mesenchymal cells that protected ALL cells from asparaginase, the St. Jude team repeated the experiment, but blocked the ability of mesenchymal cells to make the ASNS enzyme and produce asparagine. In this case, the protective effect of mesenchymal cells was eliminated. Conversely, when the researchers caused the ASNS gene to work overtime making asparagine, the ability of the mesenchymal cells layer to protect the ALL cells was significantly enhanced. The team also showed that the more actively "ASNS" genes produced ASNS in mesenchymal cells, the higher levels of asparagine they released.

Source: St. Jude Children's Research Hospital