Two-pronged approach successfully targets DNA synthesis in leukemic cells

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A novel two-pronged strategy targeting DNA synthesis can treat leukemia in mice, according to a study in *The Journal of Experimental Medicine*.

Current treatments for acute lymphoblastic leukemia (ALL), an aggressive form of blood cancer, include conventional chemotherapy drugs that inhibit DNA synthesis. These drugs are effective but have serious side effects on normal dividing tissues.

In order to replicate, cells must make copies of their DNA, which is made up of building blocks called deoxyribonucleotide triphosphates (dNTPs). Cells can either make dNTPs from scratch (the "de novo" pathway) or by picking up the breakdown products of cells death (the "salvage" pathway). Caius Radu and colleagues at the University of California, Los Angeles now show that blocking the de novo pathway using thymidine causes leukemia cells to switch to the salvage pathway. This may explain why thymidine showed limited effectiveness as a single agent in clinical trials. Blocking both the de novo and salvage pathways was lethal for leukemic cells. The authors also found that a novel small molecule inhibitor of the salvage pathway enzyme deoxycytidine kinase blocked leukemia growth in mice in combination with thymidine (to inhibit the de novo pathway). Importantly, there was no significant toxicity to normal blood cell development. Why leukemic cells and normal blood cell precursors respond so differently to this treatment requires further investigation.

According to Radu, "this new dual targeting approach shows that we can overcome the redundancy in DNA synthesis in ALL cells and identifies a potential target for metabolic intervention in ALL, and possibly in other hematological cancers."

This interdisciplinary study not only advances our understanding of DNA synthesis in leukemic cells but also identifies targeted metabolic intervention as a new therapeutic approach in ALL. Clinical trials will be required to establish whether these promising findings will translate into a new therapeutic approach for ALL.

More information: Nathanson, D.A., et al. 2014. J. Exp. Med. DOI: 10.1084/jem.20131738

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