Researchers Find Way to Overcome Drug Resistance in Leukemia

The findings hold particular promise for people who haven't been helped by the targeted drug tagraxofusp.

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Dana-Farber scientists had a perfectly reasonable theory of why acute myeloid leukemia (AML) and blastic plasmacytoid dendritic cell neoplasm (BPDCN) sometimes become resistant to the targeted drug tagraxofusp. Cancer, however, can flout even the best theories.

An account of the discovery of the true source of resistance to the drug — and the identification of a drug that may overcome that resistance — appears in a recent issue of the Journal of Clinical Investigation. The findings hold particular promise for patients with either disease who haven't been helped by tagraxofusp, which has been approved for the treatment of BPDCN and is currently being tested in other blood-related cancers. (BPDCN is a rare, aggressive malignancy of the bone marrow and blood that is most common in patients 60 years and older.)

The new research involved a careful scrutiny of tagraxofusp's effect on cancer cells. One of the distinguishing features of hematologic cancer cells, including AML and BPDCN, is an abundance of a protein called CD123 on the cell surface. The protein is part of the docking site for interleukin-3 (or IL3), a substance that stimulates white blood cells to grow and divide. The more CD123 a cell has, the more ebulliently it responds to IL3's growth signals.

CD123 is the particular target of tagraxofusp, which is a "conjugate" drug consisting of IL3 fused to a shortened version of the diphtheria toxin, the disease-causing product of the diphtheria bacterium. The drug works like a guided missile with a poison payload: The IL3 portion carries the toxin to cancer cells and essentially gives them a case of diphtheria. The cells die of an inability to make needed proteins.

One might think that the most likely cause of tagraxofusp resistance would be that tumor cells lose their CD123: Without a target to latch onto, the drug can't deliver its knockout blow to the cells. When investigators examined tagraxofusp-resistant cells from patients with AML and BPDCN, however, they found CD123 aplenty.

"We made experimental models of cells resistant to the drug and found that they, too, didn't lose CD123," says the study's senior author Andrew Lane, MD, PhD, director of the BPDCN Center at

Dana-Farber. “We could show that the diphtheria toxin was getting into the cells, but it wasn’t killing them.”

Instead of being able to dodge a visit from tagraxofusp, the cells had become resistant to the diphtheria toxin itself. A series of experiments revealed how.

Tagraxofusp resistance, it turns out, begins in a hitch in a cell mechanism called the diphthamide synthesis pathway. Researchers found the particular culprit to be an underactive gene in the pathway called DPH1.

The protein made from DPH1 is responsible for making a subtle change in the composition of a protein known as eEF2, swapping one of eEF2’s component parts — an amino acid — for another. And it’s here, on eEF2, where a shortfall in the DPH1 protein results in resistance to the diphtheria toxin.

eEF2 is a vital part of the cell’s machinery for making proteins, the chains of amino acids that do much of the work needed to keep cells alive and intact. The diphtheria toxin attaches pieces of sugar molecules to eEF2, hampering the production of proteins and ultimately leading to the cell’s death. It so happens that the DPH1 protein changes an amino acid at the exact spot on eEF2 where the diphtheria toxin would ordinarily affix a sugar molecule. That change — one of the most minor alterations that can occur within a protein — is enough to prevent the diphtheria toxin from pasting on a piece of sugar and stymying eEF2. Unhindered, eEF2 continues to function, and the cancer cell, now tagraxofusp-resistant, lives on.

The discovery suggested a way to overcome such resistance. The abnormally low activity of the DPH1 gene in AML and BPDCN is due to a process called DNA methylation, in which chemical units called methyl groups are attached to sections of the gene, decreasing production of the DPH1 protein. As luck would have it, a drug capable of blocking such methylation, named azacytidine, already exists.

Researchers treated tagraxofusp-resistant cancer cells with azacytidine and found, as expected, that it revived the activity of DPH1 and made the cells vulnerable to tagraxofusp. When they tested a combination of tagraxofusp and azacytidine in models of human AML and BPDCN, the duo drove the disease into remission.

Success in the laboratory and in model systems spurred Dana-Farber investigators to launch a phase I clinical trial of the combination in patients with AML or high-risk myelodysplastic syndromes.

“We are particularly proud of how rapidly our laboratory discoveries were used to design a new clinical trial to expand the drug’s benefit to more patients with leukemia,” Lane remarks. “Progress from clinic to lab back to clinic is only possible because of cooperative research and patient care at Dana-Farber.”

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