Epigenetic pathway and new drug show promise in reversing a hard-to-treat childhood cancer

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A difficult-to-treat form of childhood leukemia relies on changes in the structure of DNA – so-called epigenetic changes – to wreak genomic havoc within white blood cells, according to one of two studies conducted by a research team at Children's Hospital Boston and Dana-Farber Cancer Institute. Together with collaborators from a biotechnology company, the same team also showed that a new drug that blocks these changes could deactivate cancer-promoting genes and halt the growth of this cancer.

These studies, reported in a pair of papers in the July 11, 2011 issue of *Cancer Cell*, are the first to therapeutically target a core epigenetic vulnerability in the subgroup of leukemias caused by a "reshuffling" or rearrangement of the mixed lineage leukemia (MLL) gene.

"We have known for a while that MLL leukemias arise from widespread alterations not in the genetic code itself, but in the structure of the DNA and the proteins associated with it," according to Scott Armstrong, MD, PhD, a pediatric oncologist at Children's and Dana-Farber. "We now show that these epigenetic changes indeed turn on cancer-promoting genes within white blood cells, and ultimately cause the leukemia.

"Even more importantly," he continued, "we show that we can reverse the process."

While childhood leukemia is one of the great success stories in cancer therapy, those caused by MLL gene rearrangements stand out as devastating exceptions. In these cancers, a portion of chromosome 11 (where the MLL gene resides) breaks off and fuses with parts of other chromosomes to create new fusion proteins. The fusion proteins subvert the normal function of the MLL gene and activate a set of leukemia-causing genes.

MLL gene rearrangements account for approximately 10 percent of children and adults diagnosed with acute lymphoblastic or acute myeloid leukemias; most of these patients do not respond well to standard leukemia treatments.

"The success rates for treating other childhood leukemias has reached 80 or 90 percent," Armstrong said. "However, we still only achieve about 50 percent success in treating MLL-rearranged leukemias. We need to find better ways of caring for these patients, and these results give us confidence that we are heading in the right direction."

Armstrong had previously shown that MLL-rearranged leukemia cells have a unique pattern of histone methylation, a specific kind of epigenetic modification, caused by an enzyme called Dot1l. This enzyme, which is recruited to cancer-promoting genes by the MLL-fusion protein, attaches a methyl group to a particular amino acid on a histone (a scaffolding protein that helps manage gene activation) called histone H3.

In the first of the two *Cancer Cell* papers, Armstrong, along with Kathrin Bernt, MD, and Andrew Kung, MD, PhD, of Children's and Dana-Farber, confirms that genes targeted by a MLL fusion protein called MLL-AF9 are associated with inappropriately methylated histone H3 proteins. By genetically inactivating Dot1l, the team could eliminate the MLL-specific histone methylation and gene expression patterns in cells

from a mouse model of the disease. In addition, they found that mice injected with leukemia cells lacking Dot1l did not develop leukemia, in contrast to those injected with leukemia cells possessing active Dot1l.

"Our previous work suggested that Dot1l was the culprit behind the abnormal methylation patterns in MLL-rearranged cells," Armstrong noted. "We now know that these leukemias fully rely on this enzyme and the methylation pattern it generates in order to persist and grow.

"While methylation tags on histones are very difficult to manipulate directly," he added, "Dot1l is much easier to target therapeutically."

The second *Cancer Cell* paper, co-authored by Armstrong, Bernt, Kung and collaborators at the biotechnology company Epizyme, takes the Dot1l findings a step further by showing that a small molecule called EPZ004777, which inhibits the enzyme, does indeed eliminate the abnormal methylation pattern in MLL cells. In cell-based laboratory models, the effects of treatment with EPZ004777 mirrored those obtained by inactivating Dot1l in genetically engineered "knockout" mice, while selectively causing MLL-rearranged leukemia cells to die off in about two weeks' time. Moreover, mice with MLL-rearranged leukemia showed increased survival when treated with EPZ004777.

"The oncology field is very excited about epigenetic inhibition right now," Armstrong said. "Enzymes like Dot1l that influence epigenetics are overactive in many cancers. What we've done is show that we can block one of these enzymes and get very specific anti-tumor activity in a previously very hard-to-treat disease."

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