The good and bad side of anti-cancer compounds

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Compounds known as “HDAC inhibitors” exhibit cancer-killing activities in cultured cells. While they are currently being tested as anti-cancer agents in clinical trials, just how they execute their effects is unclear.

In a pair of recent papers, Vanderbilt-Ingram Cancer Center investigators provide a potential mechanism by which HDAC inhibitors specifically damage cancer cells and offer clues about possible adverse effects of these compounds – findings with important implications for their clinical use as cancer therapies.

Scott Hiebert, Ph.D., professor of Biochemistry and Medicine, and colleagues initially set out to study how chromosomal translocations – which happen when chromosomes break and rejoin, creating new genes at the breakpoints – cause acute leukemias.

He previously had found that a chromosomal translocation common in acute myeloid leukemias led to the formation of a new protein, a mutant transcription factor, that actively turned genes off. Enzymes known as histone deacetylases (HDACs) helped the mutant protein turn genes off by stabilizing the tightly coiled structure of DNA in chromosomes, making it inaccessible to proteins that transcribe DNA.

“We thought that if we could inhibit these HDACs, we could turn the genes back on and cure leukemia,” Hiebert explained.

While there are at least 17 different HDACs, Hiebert's work suggested that one in particular, called HDAC3, might be the critical HDAC in triggering acute leukemia.

To investigate the effects of inhibiting HDAC3, Hiebert and colleagues genetically engineered mice lacking the protein. However, the mice died before birth. Even when grown in cell culture, mouse cells lacking HDAC3 died.

"The question is: why are they dying? And what we found was kind of surprising," he said.

In the April 11 issue of Molecular Cell, Hiebert and colleagues report that these cells die because they can't repair the DNA damage that occurs naturally when the cells copy their DNA during cell division. HDAC3 inhibition only killed cells that were in the process of DNA replication. However, cells cultured in a medium that stalled cell division – a situation similar to the mature cells in most adult tissues – survived.

This provided an important clue as to why HDAC inhibitors specifically kill tumor cells – which divide rapidly and prolifically – and spare healthy cells.

"If we take cells out of the cycle, making them quiescent, like most of your tissue cells are, they aren't affected by (HDAC inhibitors) or by the (genetic) inactivation of HDAC3. Whereas cells that are actively cycling or dividing, like the tumor cell, are susceptible," said Hiebert.

"We think that these HDAC inhibitors are actually having a therapeutic benefit against cancer by causing DNA damage…and we're not repairing that damage. That eventually leads the cell to die," he explained.

Although previous studies suggest that HDAC inhibitors have some

tumor-killing ability on their own, Hiebert's recent findings especially support using HDAC inhibitors as adjuncts to chemotherapy or radiation treatment, both of which induce DNA damage. Giving an HDAC inhibitor beforehand may prevent tumor cells from being able to repair the DNA damage that will be inflicted by the radiation or chemotherapy treatments.

"We're excited about that because that's where the real benefit of these drugs will eventually come in," he says.

HDAC inhibition isn't without side effects, however. And another recent paper from Hiebert's lab, published in the *EMBO Journal* in March, provides some insight into how HDAC inhibition might cause liver damage.

In that study, Hiebert's group turned off HDAC3 in the liver only. These mice, which did survive to adulthood, developed extensive liver damage with grossly enlarged and fatty livers. The mice also had major metabolic abnormalities, reflected in elevated cholesterol and triglyceride levels.

Fortunately, the HDAC inhibitors currently under investigation are short-lived in the body, which may limit any potential adverse effects.

"I think the short half-life in people is actually going to be a benefit for these compounds, because they are transient therapies," he noted.

Hiebert's lab is following these mice to determine the long-term effects of HDAC inhibition. And, because the available HDAC inhibitors are relatively broad-spectrum, inhibiting several of the 17 HDACs, he is looking to develop HDAC inhibitors that more selectively target HDAC3.

The Food and Drug Administration recently approved an HDAC inhibitor called SAHA (suberoylanilide hydroxamic acid) for treating a form of T-cell lymphoma – which means that the drug will likely be given off-label for other types of tumors.

While this marks a major step forward in the therapeutic use of HDAC inhibitors, Hiebert notes, “we think they can be used better. And that’s why we’re excited by these results.”

Source: Vanderbilt University