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Research predicts how cancers will respond to chemo, rewrites old theory of why chemo works

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Challenging a half-century-old theory about why chemotherapy agents target cancer, scientists at Dana-Farber Cancer Institute have devised a test that can predict how effective the drugs will be by determining whether a patient's tumor cells are already "primed" for death.

In a study published online by the journal *Science* on Oct. 27, the researchers report that cancer cells that are on the verge of self-destruction are more likely to succumb to certain chemotherapy agents than cancer cells that have yet to reach that stage. The discovery suggests that it may be possible to predict which cancer patients are most likely to benefit from chemotherapy, as well as to make chemotherapy drugs more effective by pushing tumor cells closer to the point of suicide.

"Many chemotherapy agents work by damaging structures within cancer cells, particularly DNA and microtubules [tiny tubes used for a variety of cell functions]," says the study's senior author, Anthony Letai, MD, PhD, of Dana-Farber. "When the damage becomes so extensive it can't be repaired, the cells initiate a process known as apoptosis, in which they sacrifice themselves to avoid passing the damage on to their descendants."

The researchers found that cancer cells that are closer to this apoptotic threshold are more susceptible to chemotherapy than other cancer cells -- and that it's possible to measure how close cells are to that breaking

point.

Letai and his colleagues developed a technique called BH3 profiling to make that measurement. The technique focuses on mitochondria -- cell structures where the decision is made whether or not to die -- and proteins known as the BCL-2 family. Within the mitochondria, BCL-2 proteins act like bickering in-laws, some promoting apoptosis, others resisting it. The faction that predominates determines whether the cell lives or embarks on apoptosis.

The measuring technique uses bits of protein known as BH3 peptides from members of the BCL-2 family that spur apoptosis. Scientists prepare cells to allow entry of these BH3 molecules and examine whether holes begin forming in the mitochondria, a key step in apoptosis. A fluorescent dye enables scientists to measure whether the holes are forming. By adding BH3 peptides to the samples and measuring how much was needed to kill the cells, the investigators could gauge how close the cells were to apoptosis. Cells that needed the least BH3 peptide to be nudged into the suicide program were considered primed for death.

In the study, researchers first used the technique in myeloma cells from patients who were about to receive chemotherapy. "We found a high correlation between the cancer cells that were most highly primed and those that were most susceptible to chemotherapy," Letai states. The researchers went on to study tumors from 85 patients -- multiple myelomas, acute myelogenous leukemias, acute lymphoblastic leukemias, and ovarian cancers -- and in each case found the same connection: Chemotherapy proved to be most successful in the tumors that had the greatest mitochondrial priming.

The findings suggest that the conventional wisdom about why cancer chemotherapy works needs to be reconsidered, the study authors say.

The traditional explanation -- that chemotherapy targets fast-growing cells such as cancer cells -- has some merit, Letai remarks, but it has never been entirely satisfactory from a scientific viewpoint. For one, there are several types of fast-growing cancers that are not responsive to chemotherapy agents, and several types of slow-growing cancers that are. Moreover, although chemotherapy is notorious for attacking fast-growing normal cells such as the bone marrow and those in the digestive tract, there are many types of cells that turn over rapidly -- such as those in the skin -- that it doesn't harm.

Though widely accepted, Letai says the traditional explanation "was never tested as thoroughly as one would like for something that serves as a linchpin of cancer treatment." The new thinking, while not absolutely refuting the old, indicates the reasons for chemotherapy's success are more complex than generally thought.

The next step for researchers will be to test additional types of cancers to see if the connection between mitochondrial priming and chemotherapy effectiveness is valid for them as well. In addition, Letai's group wants to test in clinical trials whether BH3 profiling can be used to help oncologists better choose therapies for patients.

"One of the goals of personalized medicine is to know, in advance, which agents are likely to be effective in a given patient and which are not," Letai remarks. "This research highlights that potential."

Provided by Dana-Farber Cancer Institute