Measuring enzyme levels in cancer patients may reveal healthy cells' ability to survive chemotherapy

April 5 2013, by Anne Trafton

Credit: NATIONAL CANCER INSTITUTE

New research from MIT may allow scientists to develop a test that can predict the severity of side effects of some common chemotherapy

agents in individual patients, allowing doctors to tailor treatments to minimize the damage.

The study focused on powerful cancer drugs known as alkylating agents, which damage DNA by attaching molecules containing carbon atoms to it. Found in tobacco smoke and in byproducts of fuel combustion, these compounds can actually cause cancer. However, because they can kill tumor cells, very reactive alkylating agents are also used to treat cancer.

The new paper, which appears in the April 4 issue of the journal *PLoS Genetics*, reveals that the amount of cellular damage that alkylating agents produce in healthy tissues can depend on how much of a certain DNA-repair enzyme is present in those cells. Levels of this enzyme, known as Aag, vary widely among different tissues within an individual, and among different individuals.

Leona Samson, a member of MIT's Center for Environmental Health Sciences and the David H. Koch Institute for Integrative Cancer Research, is the senior author of the paper. She has previously shown that when alkylating agents damage DNA, the Aag enzyme is called into action as part of a DNA-repair process known as base excision repair. Aag cuts out the DNA base that is damaged, and other enzymes cleave the DNA sugar-phosphate backbone, trim the DNA ends and then fill in the empty spot with new DNA.

In this work, the researchers studied mice engineered to produce varying levels of Aag over a 10- to 15-fold range. This is similar to the natural range found in the human population.

The mice with increased levels of Aag resembled normal mice in their lifespan and likelihood of developing cancer, says Jennifer Calvo, a research scientist in Samson's lab and lead author of the paper. However, "we found drastic differences when we started challenging them with

these alkylating agents," she says.

Mice with excessive or even normal levels of the Aag enzyme showed much greater levels of cell death in certain tissues after being treated with alkylating agents.

"It's counterintuitive that extra DNA-repair capacity, or even the normal level, is bad for you," says Samson, who is a professor of biological engineering and biology at MIT. "It seems that you can have too much of a good thing."

A fine balance

It appears that too much Aag can upset the balance in the base excision repair pathway, the researchers say. This pathway involves several steps, some of which produce intermediates that can be extremely toxic to the cell if they do not promptly move to the next step. The researchers theorize that when Aag is too active, these toxic intermediates build up and destroy the cell.

Certain organs appear more vulnerable to this Aag-mediated tissue damage—in particular, the retina, pancreas, cerebellum and bone marrow—and the tissue damage is specific to certain types of cells within those tissues. Samson says all of the cells are likely experiencing similar DNA damage, but for some reason they don't all respond the same way.

"It's a very cell-specific phenomenon," she says. "We haven't completely gotten to the bottom of what it is that makes some cells behave in a certain way when they make zero or extra of a certain enzyme."

That kind of specificity has not been seen before, notes Samuel Wilson, a principal investigator at the National Institute of Environmental Health

Sciences. "It points to a different dynamic for base-lesion repair in different tissues," says Wilson, who was not involved in the research. "That fundamental question of why there are tissue-specific differences would be very interesting to follow up on."

The researchers found that an enzyme called Parp1 also plays an important role in Aag-related tissue damage. Parp1 helps to promote the repair of single-stranded breaks in DNA; such breaks are readily produced after Aag cuts out a damaged base. When Parp1 recognizes such a break, it starts to coat itself with chains of molecules called PolyADP-ribose, which then helps to recruit some of the additional proteins needed to continue the repair process.

When there is too much Aag, Parp1 becomes overactive and begins to deplete the cell's stores of NAD and ATP, which are critical for energy transfer in cells. Without enough NAD and ATP, the cell goes into an energetic crisis and dies.

Measuring levels of Aag, Parp1 and other enzymes before chemotherapy could be useful for doctors, not only to minimize side effects but also to maximize drugs' effects on cancer cells, Samson says.

"Aag is just one of many enzymes that you'd probably want to know the level of, and in the end make some kind of matrix to determine what the therapeutic window would be," she says. "We're trying to develop ways of measuring the activity of a whole battery of different DNA repair pathways in one mega-assay."

This story is republished courtesy of MIT News (web.mit.edu/newsoffice/), a popular site that covers news about MIT research, innovation and teaching.

Provided by Massachusetts Institute of Technology