Surprising culprit behind chemo resistance in rare cancer

July 2 2012

Researchers at Washington University School of Medicine in St. Louis have shown how an aggressive form of multiple myeloma resists chemotherapy.

Multiple myeloma is a rare cancer of plasma cells in the bone marrow. Though the finding has no immediate benefit for patients, the scientists say it could help guide research into better treatments.

The results appear online July 2 in the Journal of Clinical Investigation.

About 20 percent of patients with multiple myeloma have a specific genetic abnormality that is associated with a poor prognosis. Patients with this "translocation" — in which a broken section of chromosome 14 is swapped into chromosome 4 — show resistance to certain chemotherapy drugs and shorter survival than multiple myeloma patients without this particular translocation.

"Even in this cancer that has no cure, patients with the 4, 14 translocation tend to do very poorly with treatment," says Michael H. Tomasson, MD, associate professor of medicine. "But no one really knew why. For a number of years, we have been studying the gene at the chromosome's breakpoint, without much success in explaining how it could lead to cancer."

The gene at the breakpoint, called WHSC1, makes proteins that guide how DNA is packaged, an important method for regulating which genes

are turned on or off in a given cell. This type of gene is a prime suspect in cancer because an error in DNA packaging could lead to uncontrolled cell division. Patients with this translocation also make the gene's proteins in extremely high amounts, another hallmark of cancer. But even after extensive experiments, the researchers couldn't show how these proteins might make a cell cancerous.

"So we took a step back and asked what's missing?" Tomasson says. "What is different between what we're doing in the lab and what is going on with our patients?"

In the lab, they had used common techniques that only examine the small portion of the WHSC1 gene that codes for proteins. Patients, of course, are living with the entire gene. In this case, the missing piece of the puzzle lay in the so-called non-coding regions of the gene. Tomasson and his colleagues designed an unbiased method to examine these non-coding regions, specifically measuring the RNA made by the gene. RNA is closely related to DNA and plays broad roles in regulating cellular processes.

"It turns out, hidden inside this gene is a non-coding RNA that's expressed at very high levels in patients with the translocation," Tomasson says.

This particular RNA is called ACA11 and is classified as a small nucleolar RNA, or snoRNA. Generally, snoRNAs are well known only for helping the cell regulate other RNAs.

In an interesting twist, fellow Washington University researcher Jean E. Schaffer, MD, the Virginia Minnich Distinguished Professor of Medicine, had recently found the first evidence that snoRNAs are not limited to their previously defined roles. Schaffer and her colleagues showed that some snoRNAs are also involved in the cellular damage seen

in metabolic diseases such as diabetes. Reporting in *Cell Metabolism* last year, they demonstrated that some snoRNAs regulate how a cell responds to oxidative stress, stress caused by highly reactive molecules that contain oxygen.

"Jean published a paper showing that another type of snoRNA modified oxidative stress not in cancer, but in cardiac metabolism," Tomasson says. "That put us on to the idea that perhaps our snoRNA, ACA11, is also regulating the oxidative stress that can damage cells."

The scientists performed a wide variety of experiments examining ACA11 levels and oxidative stress in cancer cells. Specifically, as the amount of ACA11 went up (as it does in patients with the 4, 14 translocation), levels of reactive oxygen species that damage cells went down. As a result, the cancer cells were protected from damage. Cell proliferation increased, and these cells showed resistance to chemotherapy. Likewise, when they caused ACA11 levels to go down, the amount of reactive oxygen species increased. Within this more hostile environment, cell proliferation decreased and the cancer cells were more vulnerable to chemotherapy.

"ACA11 appears to protect the cancer cells from damaging stress," Tomasson says. "It allows the cells to grow better and be resistant to chemotherapy. And if you look at multiple myeloma patients with the 4, 14 translocation, they tend to show resistance to treatment as well. Not to every chemotherapy, but they show resistance to a number of them."

Importantly, Tomasson points out that ACA11 is present in all the cancer cells of patients with the 4, 14 translocation. It is also highly expressed in other cancers including brain, esophageal, bladder and colon cancers. And it can be found in multiple myeloma patients who do not have the 4, 14 translocation, though more rarely. As such, Tomasson says ACA11 may prove important in developing new cancer therapeutics in the

future.

"We can look for drugs that attack this mechanism," he says. "We don't yet have these drugs or other answers to know what will work well for these patients. But this is an important clue that tells us where to look."

More immediately, he says this work may provide a rationale for avoiding the chemotherapy drugs that are known to be ineffective in this group of patients.

"Now we have an angle for just focusing on the drugs that we know work better, as well as on experimental approaches for these patients," he says. "It gives us a new way to study how we can improve their care."

More information: Chu L, Su MY, Maggi Jr. LB, Lu L, Mullins C, Crosby S, Huang G, Chng WJ, Vij R, Tomasson MH. Multiple myeloma-associated translocation activates orphan snoRNA ACA11 to suppress oxidative stress. *Journal of Clinical Investigation*. Online July 2, 2012.

Michel CI, Holley CL, Scruggs BS, Sidhu R, Brookheart RT, Listenberger LL, Behlke MA, Ory DS, Schaffer JE. Small nucleolar RNAs U32a, U33 and U35a are critical mediators of metabolic stress. *Cell Metabolism*. July 2011.

Provided by Washington University School of Medicine