Study: Heart damage after chemo linked to stress in cardiac cells

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Blocking a protein in the heart that is produced under stressful conditions could be a strategy to prevent cardiac damage that results from chemotherapy, a new study suggests.

Previous research has suggested that up to a quarter of patients who receive the common chemotherapy drug doxorubicin are at risk of developing heart failure later in life. Exactly how that heart damage is done remains unclear.

In this study, scientists identified a protein called heat shock factor-1 (HSF-1) as a likely source of chemotherapy-related heart damage in mice and cell cultures. Heat shock factor-1 is known to be induced by stress - in this case, the chemotherapy treatment itself.

"We have found that a simple stress-related factor could be aggravating chemotherapy's effect on the heart," said Govindasamy Ilangovan, associate professor of internal medicine at Ohio State University and senior author of the study. "The results are leading us toward the idea that any additional stress could hurt the heart more than what chemotherapy itself can do."

The researchers gave doxorubicin to two sets of mice - normal animals and mice that were genetically altered so they could not produce HSF-1. Mice without HSF-1 had healthier hearts and lived longer after the chemotherapy treatment than did normal mice.

A closer examination on the cellular level suggested that when HSF-1 is blocked in the heart, this condition allows for the activation of a gene that produces a protein to pump the chemo medicine out of heart muscle cells, preventing these cells from dying.

Ilangovan and colleagues are working to design drugs that could selectively inhibit HSF-1 in the heart as a potential additional therapy for cancer patients undergoing chemo treatment.

The research appears this week in the Proceedings of the National Academy of Sciences Online Early Edition.

Chemotherapy targets cancer cells, but it also can kill many other kinds of cells in various organs. In most cases, Ilangovan explained, organs can regenerate their cells after this damage has occurred. But cardiomyocytes, or heart muscle cells, cannot be regenerated. The loss of muscle can lead to a disorder known as dilated cardiomyopathy, which reduces the heart's pumping action and leads to heart failure.

"This work arose from that background. We are trying to identify a factor that can be targeted to prevent the cardiomyopathy," said Ilangovan, an investigator in Ohio State's Davis Heart & Lung Research Institute.

Previous research had already shown that doxorubicin leads to activation of HSF-1 in the heart. The Ohio State researchers ran a number of experiments in animals and cell cultures to establish the relationship after chemo treatment between heat shock factor-1 and the gene that helps the heart, called multidrug-resistance-1 or MDR1.

In analyses using heart muscle cells from mice with and without activation of HSF-1, the researchers observed more activation of the MDR1 gene in cells lacking the HSF-1 protein compared to normal

mouse heart cells. In addition, they demonstrated that the MDR1 gene prompted production of a protein on these heart cells' surface that actually pumped doxorubicin away from the cells.

"This was an exciting finding. When we knock out the protein, not only is the cell death pathway prevented, but it also induces a multidrug-resistant gene, which pumps the drug away from the cells," Ilangovan said. "So when HSF-1 gets activated by chemo, that leads to cardiomyocyte death. But if we knock it out, that gene comes and protects the heart."

The researchers discovered that interplay in the heart cells between HSF-1 and another protein, NF-kB, could be traced to production of the protective gene.

"They're sort of antagonizing each other. If HSF-1 is lower, the other protein becomes dominant. They compete for the same binding site, and when we knock out HSF-1, NF-kB can go freely bind and activate the MDR1 gene," Ilangovan said. That also means that when HSF-1 is present, it inhibits NF-kB and in turn prevents the protective gene from being activated.

Mice also survived longer after a doxorubicin treatment if they did not produce HSF-1, and images of their hearts showed that chemo-related damage to the heart was reduced in the genetically altered mice compared to normal mice.

The researchers also tested breast cancer cells to be sure that brief silencing of the HSF-1 protein before chemotherapy would not induce the multidrug-resistant gene in those cells, which could be a deadly turn of events.

Proper timing of HSF-1 inhibition and limiting this inhibition to the

heart are important steps in designing drugs to target it, Ilangovan said. Multiple studies of this protein have suggested that it can have both beneficial and harmful effects in the body. Researchers appear to be reaching consensus that the timing of its activation helps determine which effect it will have - if it is activated before an injury or other damaging event, HSF-1 can be protective. After an injury - in this case, doxorubicin treatment - the protein is more commonly found to be harmful.

"I foresee that perhaps a patient would take a drug to silence HSF-1 in the heart one or two days before chemotherapy. So until the chemo is cleared out, the protein would be in the knock-down stage and no damage to the heart would occur," Ilangovan said.

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