Stress before cancer therapy could help deadly cells survive treatment, lead to disease recurrence

September 21 2010, by Emily Caldwell

Patients who experience physical or psychological stress - including rigorous exercise - one or two days before a cancer treatment might be unknowingly sabotaging their therapy, new research suggests.

Stress in the body - even physical stress caused by intense exercise - activates a stress-sensitive protein that can spark a series of events that allow cancer cells to survive such treatments as chemotherapy and radiation, according to the research.

Though the study involved a series of experiments in breast cancer cell cultures, the researchers say the findings are a clear indication that cancer cells have found a way to adapt and resist treatment with the help of this stress-inducible protein.

This cancer cell survival can be traced to the presence of heat shock factor-1, which previous research has linked to stress. Ohio State University researchers first noticed that this common protein can help heart tissue survive in a toxic environment, leading the scientists to suspect that in cancer, this phenomenon could have serious consequences.

A series of experiments using breast cancer cells showed that a protein activated by the presence of heat shock factor-1 could block the process that kills cancer cells even after the cells' DNA was damaged by

radiation. The same was true when the cells were subjected to a common chemotherapy drug.

The researchers hope to develop a drug that could suppress heat shock factor-1 as a supplement to cancer therapy, but in the meantime, they recommend that patients avoid both psychological and physical stress in the days leading up to a cancer treatment.

"One of the known inducers of this factor is exercise. I am not against exercise, but the timing is critical. It looks like any intense or prolonged physical activity a couple of days before the start of cancer therapy is highly risky, and has potential to reduce the benefits of the treatment," said Govindasamy Ilangovan, lead author of the study and associate professor of internal medicine at Ohio State.

The study appears online in the journal *Molecular Cancer Research*.

Ilangovan, an investigator in Ohio State's Davis Heart and Lung Research Institute, specializes in cardiovascular medicine. But when he observed in previous research that this stress-inducible protein could salvage heart cells that otherwise were doomed to die, he collaborated with radiology specialists to test the protein's effects in cancer.

While he used breast cancer cells for this study, he suspects that the widespread presence of heat shock factor-1 in the body means the protein could have this same effect on any kind of adenocarcinoma, a class of cancer cells that originate in a gland.

Heat shock factor-1 activates a specific protein, known as Hsp27, that ends up helping the cancer cells survive, Ilangovan said.

The researchers conducted numerous experiments to observe how Hsp27 behaves in cancer cells after they undergo ultraviolet-C radiation. The

radiation is used as a model for treatments designed to kill cancer cells by damaging their DNA. In this study, the stress of the UV radiation itself also induced the heat shock factor and, subsequently, Hsp27, which reduced the cell death.

In every experiment, a heightened presence of the Hsp27 protein was associated with lower levels of other proteins that participate in the process of cell death. When the researchers introduced siRNA, a molecule that interferes with Hsp27's function, the cell death mechanism was restored.

When the breast cancer cells were treated with doxorubicin, a common chemotherapy drug, the experiment produced similar results. When the Hsp27 protein was silenced, more of the cancer cells died.

"We clearly showed that a reduction in the level of the Hsp27 protein made the cancer cells more susceptible to both treatments," Ilangovan said.

This finding suggested to the scientists that a drug with the same effects as the interference molecule could stop Hsp27 from preventing cancer cell death. No such drug currently exists, and the siRNA molecule isn't suitable for use in patients, Ilangovan said.

But the interfering molecule had a significant effect, in one experiment leading to the death of at least 60 percent of the cancer cells that had undergone UV radiation.

Among the key reactions the researchers observed was Hsp27's relationship to a protein called p21, which allows cells to pause, repair themselves and continue dividing, leading to their survival. Damage to the DNA in cancer cells should disable this step in cell division, but the research showed that the Hsp27 caused p21 to change positions in a way

that allowed for cell survival.

"It looks like a compensatory act. We are doing something to kill the cell, but cells have their own compensatory action to oppose that," Ilangovan said.

After irradiation, the levels of Hsp27 reached their height within 48 hours, suggesting that the protein is highly active in the two days following any stressful event that activates heat shock factor-1.

"The process that sets these activities in motion takes a couple of days," Ilangovan said. "It is not proven in a clinical setting, but our hypothesis leads us to strongly caution cancer patients about avoiding stress because that stress might trigger recurrence of cancer cell growth."

Provided by The Ohio State University