Ancient mechanism for coping with stresses also gives cancer a boost

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An ancient mechanism for coping with environmental stresses, including heat and toxic exposures, also helps cancerous tumors survive, reveals a new report in the Sept. 21, 2007, issue of *Cell*, a publication of Cell Press. The findings could lead to a new way to treat cancer and may also have implications for the treatment of neurodegenerative and other diseases, according to the researchers.

The scientists found that loss of the master controller of the "heat-shock response" dramatically limited the spontaneous formation of tumors in mice genetically predisposed to developing cancer, and those exposed to cancer-causing chemicals. Most importantly, they reported, depletion of the so-called heat-shock factor 1 (HSF1) in diverse previously established human cancer cell lines strongly impaired their growth and survival, while having little effect on normal cells.

"At a fundamental level, the ability of HSF1 to enable lethal malignancies is an unfortunate legacy of its ancient role in enhancing the survival of normal cells exposed to diverse acute and chronic stresses," said Susan Lindquist, a Howard Hughes investigator at the Whitehead Institute for Biomedical Research. "We expected it would have some effect on cancer, but we were surprised at the degree."

The heat-shock response is one of the most ancient and evolutionarily conserved protective mechanisms found in nature, the researchers said. While environmental insults provoke a variety of adaptive physiological responses to help organisms cope with specific stressors, the dramatic

induction of heat-shock proteins (HSPs) is an essential unifying component of most of them.

The HSPs, which are under the control of a small family of heat-shock factors (HSFs), guard against the abnormal activity of other proteins in the face of stressors such as heat and oxygen starvation. Although less well understood, Lindquist said, HSFs also influence an array of other genes involved in cell metabolism and other basic cell functions. Scientists had also long noted that HSP levels increase in many cancer cells.

"The odd thing is, apparently no one thought it was that interesting," Lindquist said. Therefore, whether the stress management proteins played a causal, supportive, or inhibitory role in cancer remained an unanswered question. "On the one hand, given its prominent role in helping cells cope with stressful insults, HSF1 might promote [cancer's formation] by facilitating cellular adaptation to the malignant lifestyle," she explained. "On the other hand, given its general role in enhancing longevity, HSF1 might assist organisms in combating malignancy."

To find out, the researchers first looked to a common mouse model of skin cancer, in which the animals' are exposed to cancer-causing chemicals. Mice unable to switch on the heat-shock response were "far more resistant" to tumor formation than normal mice were under those conditions, they found. It took the mutant mice five weeks longer to develop tumors. They were less likely to develop cancer and, when they did, had fewer and smaller tumors. The HSF1-deficient mice also lived longer.

The researchers next examined mice predisposed to develop cancer due to a deficiency of the tumor suppressor p53, the most frequently mutated gene in human cancers. Again, they found, the HSF1-deficient animals lived tumor-free for dramatically longer. Indeed, even cancer-prone

animals lacking just one working copy of HSF1 lived longer than normal animals did. Through studies in cultured mouse cells, they found further evidence that HSF1 supports the transformation to cancer by orchestrating a variety of basic cell functions, including proliferation, survival, protein synthesis, and glucose metabolism.

They then examined the role of HSF1 in normal and cancerous human cells, including those derived from the breast, prostate, and cervix. In every case, they found that the cancerous cells, but not the normal cells, were strongly affected by HSF1's inhibition. Those findings led them to conclude that "HSF1 function helps to maintain the growth and survival of human cancer cells with diverse underlying malignant defects."

The results may have therapeutic implications, the researcher said, as an expanding array of small, drug-like compounds with potent effects on HSF1 are now becoming available. Indeed, drugs that ramp up the heat-shock response are being explored for treating ischemic injury and neurodegenerative diseases, including Huntington's and Parkinson's diseases.

The new findings raise concern that such therapies might increase the risk of cancer, Lindquist said. On the other hand, treatments designed to block HSF1 might "provide a multifaceted and broadly effective cancer chemopreventative as well as chemotherapeutic strategy."

The results also point to the delicate balance between aging, longevity, and cancer risk, she added.

"Strikingly, our data now make clear that HSF1 plays opposite roles in the complex diseases that plague aging populations," she said. "It powerfully potentiates the development of cancers. But it has also been implicated in protection against ischemia/re-perfusion injury, neurodegenerative disorders and in other broad-ranging physiological

processes affecting lifespan. We are poised on the balance between aging and degeneration [on one side] and the active, youthful cell growth, [which can lead to cancer], on the other. If we pay more attention and learn how to manipulate these systems properly, we could have a huge impact on human disease."

Source: Cell Press