Sidestepping cancer's chaperone

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Cancerous tumors are wildly unfavorable environments. Struggling for oxygen and nutrients while being bombarded by the body's defense systems, tumor cells in fact require sophisticated adaptations to survive and grow. For decades, scientists have sought ways to circumvent these adaptations to destroy cancer. Now, researchers at the University of Massachusetts Medical School (UMMS), have defined a method to target and kill cancer's "chaperone"—a protein that promotes tumor cell stability and survival—without damaging healthy cells nearby.

In "Regulation of Tumor Cell Mitochondrial Homeostasis by an Organelle-Specific Hsp90 Chaperone Network," published in the October 19 issue of *Cell*, Dario C. Altieri, MD, the Eleanor Eustis Farrington Chair in Cancer Research and professor and chair of cancer biology, and colleagues at UMMS, identify a new pathway by which cancer cells grow and survive—and provide a clear blueprint for the design and production of a novel class of anticancer agents aimed squarely at that pathway.

While previous research has demonstrated that a class of proteins known as molecular chaperones promote tumor cell survival, the specific way in which the proteins achieve this has not been well understood. And although inhibitors of a specific chaperone known as heat shock protein 90 (Hsp90) have been studied for the treatment of cancer, progress has been questionable. In this current research, Dr. Altieri and colleagues sought to both define the mechanism by which Hsp90 leads to tumor cell stability and survival, and understand why general suppression of Hsp90 has not been as successful in clinical trials.

Notably, they found a very abundant pool of Hsp90 (and its related molecule TRAP-1) in the mitochondria of tumor cells. Mitochondria are organelles that produce a cell's energy, but also play a key role in cell death. Indeed, many current drugs and treatments work by damaging the mitochondria. Data obtained by Altieri and colleagues indicate that Hsp90 and TRAP-1 protect mitochondria in tumor cells from fulfilling their role in cell death. Significantly, the increased levels of Hsp90 and TRAP-1 were found only in the mitochondria of tumor cells—not in those of normal cells.

"We have identified this mitochondrial accumulation of Hsp90 and TRAP-1 as a critical adaptive mechanism that makes cancer cells less susceptible to the unfavorable environment of tumors, and to various anticancer agents," Altieri explained.

This new understanding of the sub-cellular location of Hsp90 and TRAP-1 in the mitochondria also answers the question as to why the current Hsp90 inhibitors—which do not penetrate the mitochondria—are not as effective as hoped in the clinic. In this study, Altieri and colleagues synthesized a new compound, modifying an existing Hsp90 inhibitor so that it was able to reach the mitochondria. When the inhibitors were able to penetrate the mitochondria, they were able to eliminate the protective function of Hsp90, and induce massive tumor cell death. Notably, because this accumulation of Hsp90 and TRAP-1 only occurs in tumor cells, drugs conceived to target Hsp90 would largely spare normal cells, minimizing or even nullifying the dramatic side effects that plague many current cancer treatments.

"This is an important discovery that opens the door to the design of a completely new class of anticancer agents," Altieri explained. "It really turns the tables on a field that has been explored with only partial success. We can now take a class of drugs and make them better and more efficacious by engineering them to accumulate in the

mitochondria.”

Source: University of Massachusetts Medical School