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Research on a rare cancer exposes possible route to new treatments

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Researchers from Huntsman Cancer Institute (HCI) at the University of Utah (U of U) discovered the unusual role of lactate in the metabolism of alveolar soft part sarcoma (ASPS), a rare, aggressive cancer that primarily affects adolescents and young adults. The study also confirmed that a fusion gene is the cancer-causing agent in this disease. The research results were published online in the journal *Cancer Cell* Nov. 26, 2014.

ASPS tumor cells contain a chromosomal translocation—strands of DNA from two chromosomes trade places. The two strands fuse together to create a new gene, ASPSCR1-TFE3 that functions differently than either "parent" gene.

For the study, Kevin B. Jones, MD, an HCI investigator and assistant professor in the Department of Orthopaedics at the U of U, and his research team activated the ASPSCR1-TFE3 gene in mice. The cancer was completely penetrant; every mouse with the activated fusion gene developed a tumor.

"The mouse tumors were remarkably similar to human ASPS tumors," said Jones. "The fusion gene not only initiates a cancer in the mouse, it initiates all the features we associate with this cancer in humans, including nearly identical RNA profiles." This is especially important in the study of sarcoma, as few human cell lines exist.

Jones said one surprising finding of the study was the location of the

tumors in mice. In humans, most ASPS tumors occur in skeletal muscle, but all the mouse tumors occurred within the skull—"not necessarily in brain tissue, but within the environment of the cranium.

"The two places where we found most of the mouse tumors—inside the brain and inside the orbit of the eye—had the highest concentrations of lactate," said Jones. "The tissues where ASPS occurs in humans, the skeletal muscles, also have high concentrations of lactate."

Most cancer cells generate their energy in a process called glycolysis, in which they rapidly but inefficiently consume glucose. This process creates lactate as a waste product that the cancer cells push out into their surroundings.

"In our study, the ASPS tumor cells absorbed lactate from their environment and used it both as a fuel and as a signaling molecule that made the cells behave as if they were in a low-oxygen environment," said Jones. "It's unusual to find a cancer using lactate this way. The ASPS cells grow preferentially where they are bathed in high concentrations of lactate."

Future work in this area could include finding ways to block the cancer cells' uptake of lactate to starve them or render them less aggressive, according to Jones. "In the broader picture of trying to understand the metabolism of cancer—the way cancer cells interact with their environment and produce energy—we can work on discovering their unique vulnerabilities," he said. "That would be the ideal route to new and effective treatments.

"When we find a translocation and fusion gene associated with a specific cancer, the question is always whether it drives the cancer or is a passenger created through the cancer's action on the tumor cells," said Jones. "Our study confirmed that the fusion gene ASPSCR1-TFE3

causes ASPS; it's the driver."

Only 50 to 100 cases of ASPS are diagnosed in the United States each year, but this research bears on a fundamental question of cancer research: How does a cancer start? Initiating most common cancers requires many genetic mistakes in the affected cells, and as the cancer grows even more mistakes are gained. Jones said that this study, as well as others looking at cancers initiated by the single event of a chromosomal translocation and the resulting fusion gene, may provide a "clearer lens through which to look at the fundamental biology of cancer's patterns of development."

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