Turning key metabolic process back on could make sarcoma more susceptible to treatment

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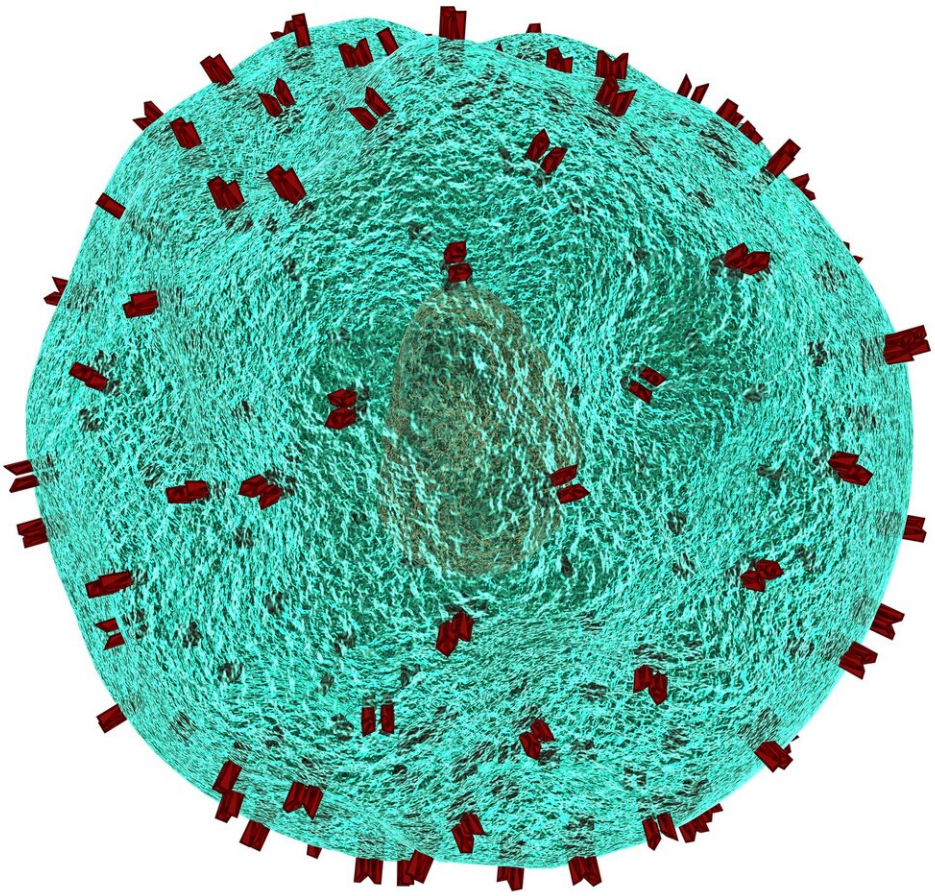

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Soft tissue sarcoma cells stop a key metabolic process which allows them to multiply and spread, and so restarting that process could leave these cancers vulnerable to a variety of treatments. The enzyme that controls the process is called FBP2, and researchers from the Abramson Cancer Center of the University of Pennsylvania, who detailed their findings in *Cell Metabolism*, also showed that manipulating sarcoma cells to ramp up FBP2 expression slows or even stops their growth entirely. This ultimately leaves them susceptible to targeted therapies and potentially takes away their ability to develop treatment resistance.

Soft tissue sarcoma is actually a collection of distinct, rare cancer types affecting tissues that connect and surround other parts of the body, including muscle, fat, tendons, nerves, and blood vessels. While they can grow anywhere, the arms, legs, chest, and stomach are the most common sites. Because these cancers appear in so many different places in the body, their biology is incredibly diverse, making it difficult to develop one targeted treatment that can be broadly effective for all patients. Currently, the best options for treatment are surgery—which may involve amputation—chemotherapy, and radiation.

"While other cancer types associated with high mutational burden have benefitted from the development of immunotherapies, the diversity and low frequency of genetic mutations in soft tissue sarcomas have made them more difficult to treat, which is why our identification of a broadly expressed metabolic approach is potentially so exciting," said the study's senior author M. Celeste Simon, Ph.D., the Arthur H. Rubenstein, MBBCh Professor of Cell and Developmental Biology in Penn's Perelman School of Medicine and scientific director of the Abramson Family Cancer Research Institute. The study's lead author is Peiwei

Huangyang, who performed the work while obtaining her Ph.D. in Simon's lab.

While FBP2 is broadly expressed in normal cells, soft tissue sarcomas have a way of dramatically suppressing it. Building on their previous work—published in Nature—showing a related pathway controlled by FBP1 serves a similar function in renal and liver cancer, Simon and her team used mouse models to show that causing soft tissue sarcoma cells to re-express FBP2 the way healthy cells do stops the cancer from growing, potentially making it more vulnerable to both targeted and immune-based therapies.

"Essentially, once they start acting like normal cells, they don't hide and grow the way cancer normally does," Simon said.

The team also found that the enzymes involved in this process are located in the cell's nucleus, meaning this pathway could stop cancer cells from adapting to their natural environment and becoming resistant to cytotoxic drugs. It's tied to the understanding of how cells respond to environmental stresses to alter their metabolism and survive, which is the work that received the 2019 Nobel Prize in Physiology or Medicine.

While this study shows the importance of FBP2, further research is needed to show that using drugs to manipulate cells to re-express FB2 will have the expected effect. Simon points out that these drugs already exist in other cancer treatments—specifically blood cancers—meaning the pipeline to translate this approach to patients should be relatively rapid if research proves it is effective.

More information: Peiwei Huangyang et al, Fructose-1,6-Bisphosphatase 2 Inhibits Sarcoma Progression by Restraining Mitochondrial Biogenesis, *Cell Metabolism* (2019). DOI: 10.1016/j.cmet.2019.10.012

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