Researchers identify how cancer cells adapt to survive harsh tumor microenvironments

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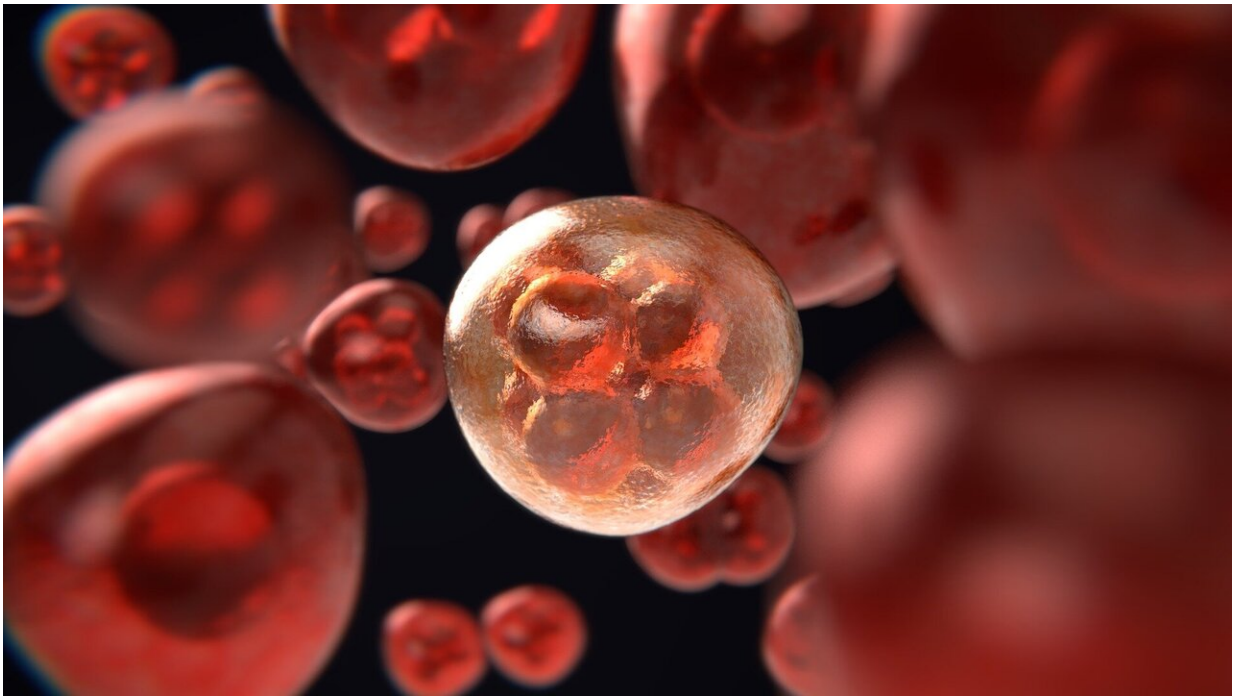

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Cells need energy to survive and thrive. Generally, if oxygen is available, cells will oxidize glucose to carbon dioxide, which is very efficient, much like burning gasoline in your car. However, even in the presence of adequate oxygen, many malignant cells choose instead to ferment glucose to lactic acid, which is a much less efficient process. This metabolic adaptation is referred to as the Warburg Effect, as it was first

described by Otto Warburg almost a century ago. Ever since, the conditions that would evolutionarily select for cells to exhibit a Warburg Effect have been in debate, as it is much less efficient and produces toxic waste products.

"The Warburg Effect is misunderstood because it doesn't make sense that a cell would ferment glucose when it could get much more energy by oxidizing it. Our current study goes to the heart of this problem by defining the microenvironmental conditions that exist in early cancers that would select for a Warburg phenotype. This is important because such cells are much more aggressive and likely to lead to cancers that are lethal," said Mehdi Damaghi, Ph.D., study first author and research scientist in the Cancer Physiology Department at Moffitt Cancer Center.

To better understand the conditions that select for the Warburg Effect and the mechanisms where cells can express this metabolic adaptation, Moffitt researchers subjected nonmalignant cells to the harsh tumor microenvironment that is present during early carcinogenesis, known as ductal carcinoma in situ (DCIS). DCIS is an uncontrolled growth of cells within the breast ducts. It is the earliest stage at which breast cancer can be diagnosed. Although it is considered noninvasive, it can lead to invasive cancer in a fraction of cases. In a new research article published in the *Proceedings of the National Academy of Sciences*, the Moffitt team shows that these conditions select for cells to express a Warburg Effect.

The investigators hypothesized that the complex interplay of factors in the harsh tumor microenvironment within DCIS, such as low nutrients, low oxygen and high acidity, may lead pre-malignant cells to express a Warburg phenotype in order to survive and thrive within these hostile conditions. To test their theory, the research team subjected low glycolytic breast cancer cells to these different microenvironment selection pressures (low oxygen, high acidity, low glucose and starvation) over 12 to 18 months. After this selection, individual clones of the

cancer cells were isolated and characterized for their metabolic and transcriptomic profiles.

Their results indicate that the poor metabolic conditions in the tumor microenvironment of DCIS lead these pre-malignant cells to select for a Warburg phenotype through transcriptional reprogramming. In particular, the researchers found that the activation and stabilization of the transcription factor, KLF4, allowed for cancer cells to adapt to a phenotype that can survive the harsh environment. "Although KLF4 is clearly responsible for this phenotype in this particular system, we expect that different cell lineages will come up with their own approaches to solve this need for metabolic adaptation. We call this 'functional equivalence,' " said Robert Gillies, Ph.D., senior author and chair of the Cancer Physiology Department. "We have shown clearly that this phenotype is selected by harsh microenvironmental conditions."

More information: Mehdi Damaghi et al, The harsh microenvironment in early breast cancer selects for a Warburg phenotype, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2011342118

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