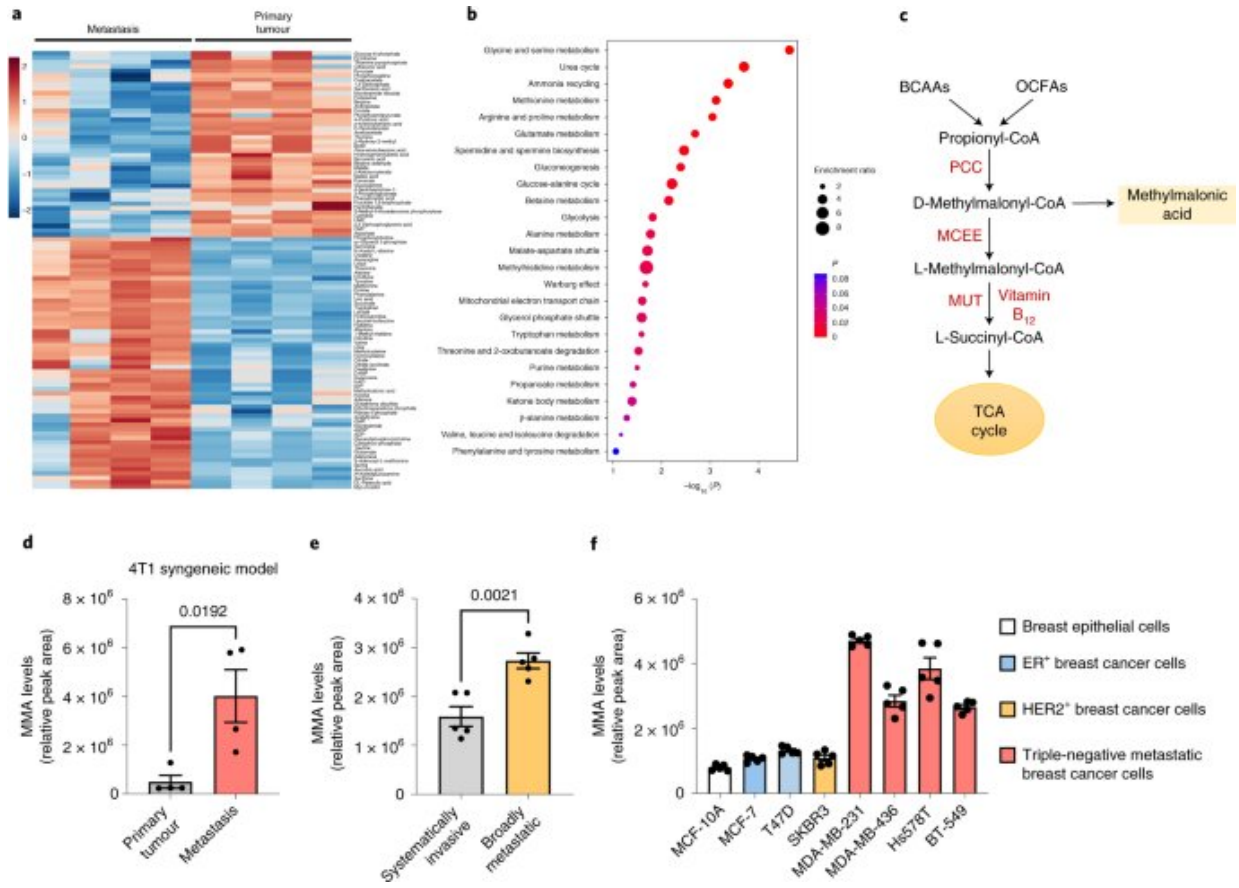
Tumors change their metabolism to spread more effectively

April 13 2022, by Alan Dove



MMA is upregulated in breast cancer metastasis. Credit: *Nature Metabolism* (2022). DOI: 10.1038/s42255-022-00553-5

Cancer cells can disrupt a metabolic pathway that breaks down fats and

proteins to boost the levels of a byproduct called methylmalonic acid, thereby driving metastasis, according to research led by scientists at Weill Cornell Medicine.

The findings open a new avenue for understanding how tumors spread to other tissues via metastasis, and hints at novel ways to block the spread of cancer by targeting the process.

The study, published March 31 in *Nature Metabolism*, shows that metastatic tumors suppress the activity of a key enzyme in propionate metabolism, the process by which cells digest certain fatty acids and protein components. Suppressing the enzyme increases production of methylmalonic acid (MMA). That, in turn, causes the cells to become more aggressive and invasive.

Cancer is the second-leading cause of death worldwide, and metastasis drives much of that mortality. Once a tumor begins to metastasize to different tissues and organs around the body, it can quickly become difficult or impossible to treat. However, researchers have made few inroads in understanding how a tumor cell acquires the ability to metastasize.

"A lot of work has been focused on primary tumor initiation and growth, or examining the metastatic tumor, but to go from the primary tumor to the metastatic tumor, that transition has not been studied very extensively," said co-senior author John Blenis, the Anna-Maria and Stephen Kellen Professor in Cancer Research, professor of pharmacology and associate director of basic science at the Sandra and Edward Meyer Cancer Center at Weill Cornell Medicine.

To address that gap, Blenis and his colleagues have worked for several years to characterize the metabolic changes that cells undergo during the metastatic transition. That effort previously revealed that as people age,

their bodies produce more serum MMA (although the source remains unknown), and that higher MMA levels drive worse cancer outcomes. Healthy cells also produce MMA, though, so in the new study, Blenis' team probed the metabolite's cancer-related activities more deeply.

"Cancer cells themselves can hijack the pathway that makes methylmalonic acid, and this forms a feed-forward cycle that drives cancer progression toward more aggressive and more metastatic forms," said co-first author Vivien Low, a postdoctoral researcher in Blenis' lab.

The other co-first authors, Ana Gomes and Didem Ilter, were also postdoctoral fellows in the lab at the time of the study. Gomes is now a faculty member and Ilter is a research scientist at H. Lee Moffitt Cancer Center & Research Institute.

The discovery adds to a growing body of work showing that specific products of metabolism, called oncometabolites, can drive many aspects of cancer progression and metastasis.

While the new paper focused on various models of breast cancer, Low said the team is also analyzing other types of cancer cells, where they expect to find similar mechanisms operating. The scientists are also searching for ways to attack the process.

"Metastasis is responsible for about 80% to 90% of cancer-related mortality," Blenis said, "so if we can predict when someone has the potential to develop metastatic tumors, or treat those metastatic tumors that might have this pathway up-regulated, then we might have a very effective, novel therapy."

More information: Ana P. Gomes et al, Altered propionate metabolism contributes to tumour progression and aggressiveness, *Nature Metabolism* (2022). DOI: 10.1038/s42255-022-00553-5

Provided by Cornell University