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Study unveils molecular pathways followed by metastatic cancer cells

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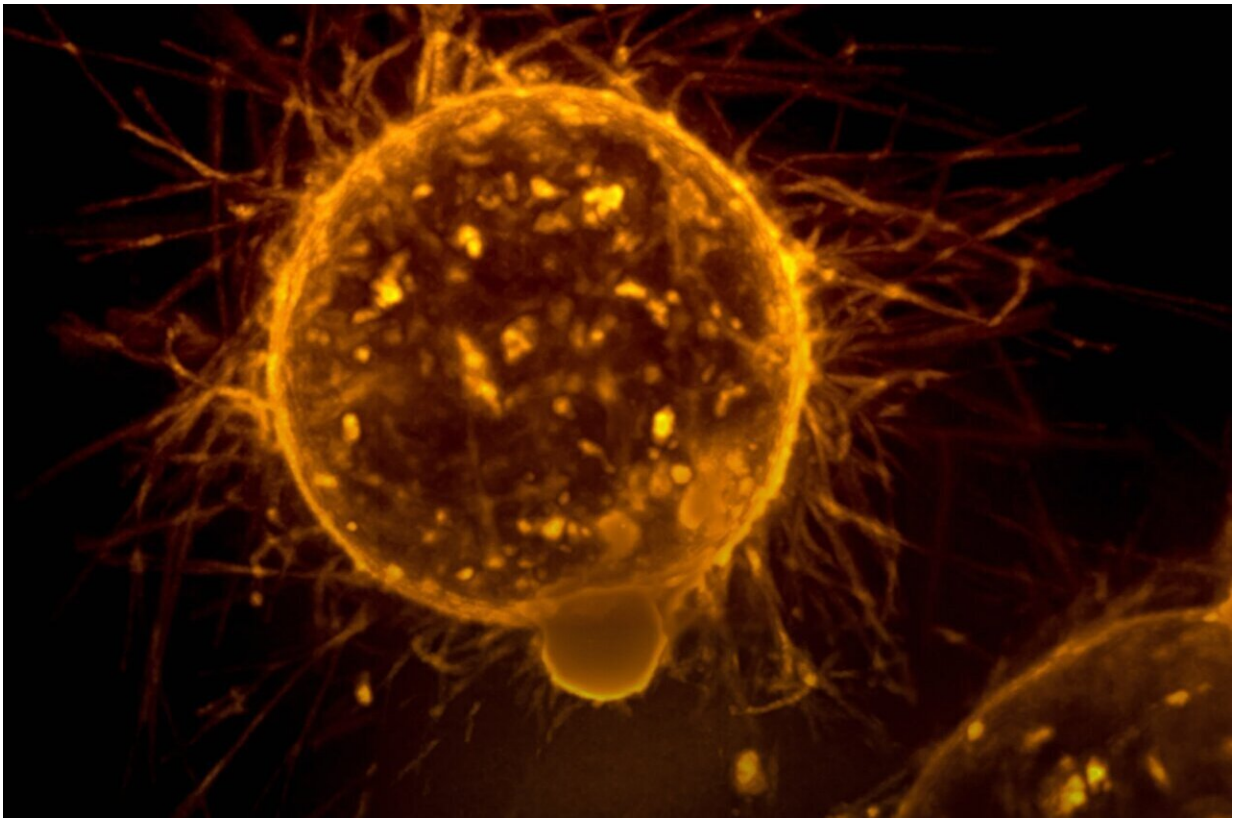

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Metastasis, the process by which cancer cells leave the primary tumor and spread to other tissues to seed new cancerous growth, causes most cancer deaths. There is a clear need to better understand the processes

that enable cancer cells to branch off, survive in a different environment and form another tumor, as new insights may illuminate novel treatment strategies.

In a new study published in the journal *Cell Reports Medicine*, a team of scientists at Baylor College of Medicine took a closer look at the molecular pathways metastatic cancer cells use and identified four cancer subtypes according to the main genes expressed. The findings unveiled potential vulnerabilities of each subtype that have relevant implications for therapy.

"We analyzed molecular data from the public domain collectively representing 38 studies and more than 3,000 patients and 4,000 tumors," said lead author Dr. Chad Creighton, professor of medicine and co-director of cancer bioinformatics at the Dan L Duncan Comprehensive Cancer Center at Baylor. "Our pan-cancer analysis looked to identify molecular pathways that are common to many different cancers, regardless of tumor origin."

One challenge when studying cancer metastasis is that tumor samples have abundant non-cancer tissue. Samples tend to be a mixture of cancer and non-cancer cells, such as normal endothelial cells, fibroblasts and immune cells, that interfere with the molecular analysis of cancer cells.

To cut through all that noise, Creighton and his colleagues worked with data obtained from PDX cancer models. In this model, human cancer tissues implanted in immune deficient mouse models grew into a new tumor similar to a metastasis.

"The nice thing with the PDX model is that mouse cells are different enough that they cannot be confused with human cells and, therefore, they are not going to contribute to the cancer profile," Creighton said.

By analyzing the data of the PDX models, the team was able to define four cancer molecular subtypes in the metastasis-like PDX samples. Importantly, the researchers determined that those four subtypes also are present in patient metastasis and are broadly represented among the different cancer types studied. These subtypes not only facilitate understanding the molecular underpinnings of metastases but also point at potential therapeutic interventions already under investigation.

The tumors in the first subtype have extensive alterations in gene copy number, higher expression of both DNA repair genes and transcription factor genes such as *MYC*. This suggests that tumors of this subtype might be susceptible to MYC-inhibiting compounds or BET inhibitors currently under clinical evaluation. The second subtype has higher expression of genes involving metabolism, prostaglandin synthesis and regulation. Tumors in this group might be susceptible to COX-2 inhibitors.

The third subtype has evidence of neuronal differentiation and high expression of genes *EZH2* and *BCL2*. In this case, such tumors might respond better to EZH2 or BCL2 inhibitors. The fourth subtype has higher expression of immune checkpoint and Notch pathway genes, suggesting that these tumors could be affected by immunotherapy.

"When comparing a primary tumor with the metastatic tumor derived from it, we found that, in most cases, the primary and the metastatic tumors were not of the same subtype," Creighton said. "This has important implications for therapy as it suggests that primary and metastatic tumors may not be treated in the same way. The findings provide valuable insights for the development of personalized treatments for metastatic cancer."

Yiqun Zhang and Fengju Chen at Baylor College of Medicine also contributed to this work.

More information: Chad J. Creighton & colleauges, Pan-cancer molecular subtypes of metastasis reveal distinct and evolving transcriptional programs, *Cell Reports Medicine* (2023). DOI: 10.1016/j.xcrm.2023.100932. www.cell.com/cell-reports-medi … 2666-3791(23)00024-1

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