How oxygen deprivation causes cancer cells to spread

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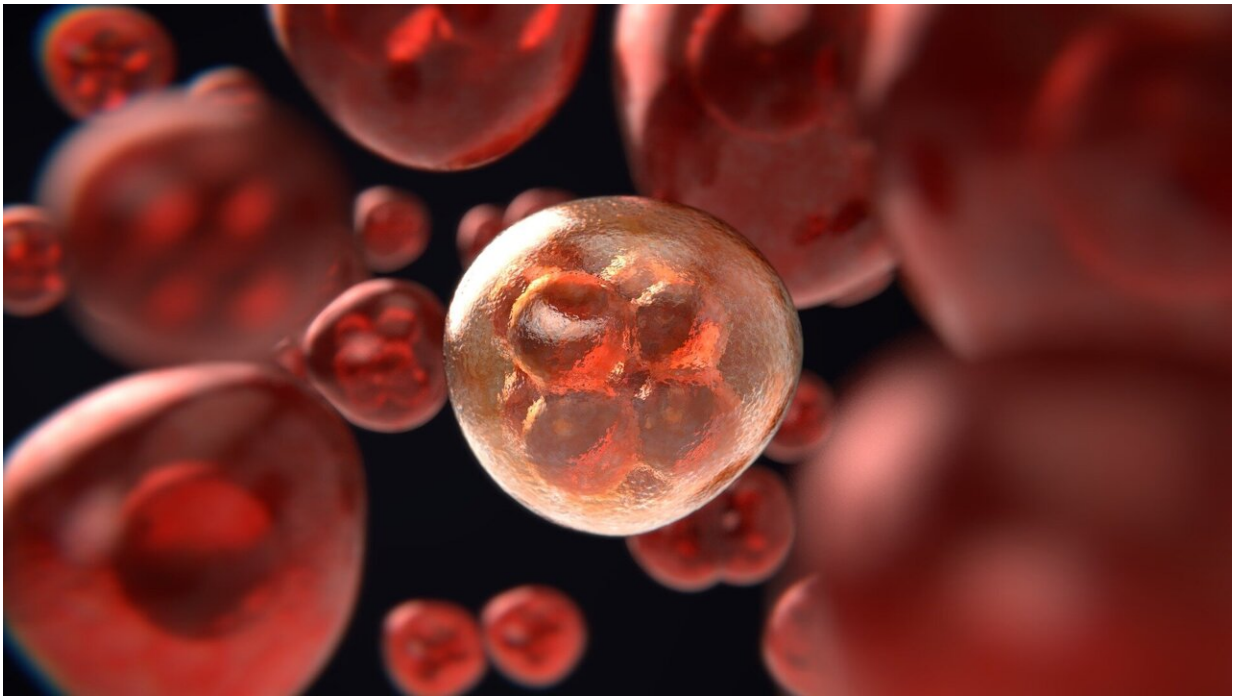

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In breast cancer, metastasis rather than the primary tumor is the cause of death. A lack of oxygen in the tumor cells promotes this metastasis, accompanied by a reprogramming of the cell's metabolism. Ph.D. candidate Qiuyu Liu investigated these alterations to get more knowledge about the actionable mechanisms driving cancer progression in different types of breast cancer. She hopes her research will

contribute to new therapies.

Cancer cells grow fast. This often causes tumors to outgrow the reach of their surrounding vascular system. This results in decreased oxygen availability, called hypoxia. "This lack of oxygen triggers several processes that promote metastasis," explains Liu. "It activates genes that promote the motility of tumor cells, and it makes it easier for cancer cells to migrate to new locations and invade new tissues. I wanted to learn more about the molecular mechanisms underlying these responses."

Why does hypoxia lead to metastasis?

Liu profiled cancer cells from distinct subtypes of breast cancer under hypoxia and investigated the role of so-called transcription factors. These are proteins that control the rate at which specific genes are activated. These activated genes translate into proteins, which can then regulate all kinds of processes in the cell.

"HIFs, or hypoxia-inducible factors, are transcription factors that respond to hypoxia. In other words: they will activate specific genes during a lack of oxygen. In cancer cells, this regards genes contributing to metastasis in different ways," says Liu.

"We were interested in the different effects of hypoxia on the different types of breast cancer, -more specifically in the crosstalk between HIFs and a protein complex called YAP/TAZ. In a variety of cancers, YAP/TAZ is often hyperactivated. In breast cancer, this hyperactivation can promote multiple features of cancer progression such as metabolism, migration and invasion of other tissues, and even chemotherapy drug resistance. It would therefore be very interesting to see whether HIFs have any effect on this YAP/TAZ complex, and whether this would enhance its working or the opposite."

Different types of breast cancer

Breast cancer can be divided into different subtypes including luminal A and B, triple-negative (basal A and B) and HER-2 positive. The classification into subtypes is based on so-called hormone receptors. These are proteins on the surface of a cell, which transmit signals from hormones outside the cell to other proteins within the cell.

In many types of breast cancer, the tumor cells have extra-large amounts of these hormone receptors. These receptors can serve as targets for medication. Hormone therapy is widely used and successful. In triple negative breast cancer, however, is that the tumor cells have very low levels of hormone receptors. As a result, existing hormone therapies have no effect, and this type of cancer has the highest metastatic ability and death rate.

Hypoxia has different effects in different types of breast cancer

Liu found distinct responses to chronic hypoxia between different types of breast cancer. "In basal breast cancer cells, hypoxia mainly affects the cell skeleton and enhances the cell migration speed, while in the luminal cells it mainly causes de cells' metabolism to change." Liu furthermore found that in basal cells, HIF mediates a process that results in decreased TAZ activity. YAP was nearly unaffected.

"Because different types of breast cancer respond differently to hypoxia, we also need to threat treat them differently. Our findings may point out actionable mechanisms that drive the progression of cancer: starting points for further research to provide insight into the distinct therapeutic strategies for the different subtypes of breast cancer. That would be great."

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