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Study finds cancer cells manipulate fat metabolism for survival

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Mayo Clinic scientists have discovered a new survival strategy used by tumour cells where they switch off fat metabolism when oxygen is low.

The study in mice, published in the journal eLife, explains how tumour cells can grow in conditions with low oxygen, and reveals a new and unique drug target that could be exploited for future cancer treatments.

Hypoxia – a lack of oxygen reaching body tissues – is a well-known hallmark of cancer. "We know that the hypoxic parts of tumours contain fat droplets, and evidence suggests that a tumour's capacity to accumulate these droplets is linked to its ability to survive in low-oxygen conditions," explains Xiaodong Zhang, Ph.D., Research Associate at Mayo Clinic's Arizona campus, US, and lead author of the study. "But we didn't understand how and why these lipid droplets form, and that's what we set out to investigate."

The team was particularly interested in the role of an enzyme molecule called adipose triglyceride lipase (ATGL) in this process because it speeds up the breakdown of fat and has also been shown to suppress tumour growth. But when they disrupted the ATGL gene in hypoxic cancer cells, they saw no further increases in droplet accumulation, so they knew it was a change to the ATGL activity that caused reduced fat breakdown.

To learn more, they searched for other protein molecules that might be involved in ATGL's activity. This led them to a molecule called HIG2,

which is abundantly present in a wide variety of solid tumours including colon and renal cancer. They found that HIG2 was co-located with ATGL, and has similar properties to another molecule known to block ATGL. They tested the effects of HIG2 on ATGL, and found that it specifically blocks fat breakdown caused by ATGL and, as a result, increases the size of fat droplets in cells. A mutant HIG2, unable to bind to ATGL, did not cause any of these effects.

The team next wanted to see whether these effects were replicated in cells with low oxygen. As hoped, HIG2 was dramatically activated in low-oxygen conditions and caused increased accumulation of fat droplets in the cells. Again, cells with mutated HIG2 showed none of these effects. However, when ATGL was also mutated, fat accumulation was restored. This proves that HIG2 works to increase fat storage and decrease fat metabolism in the cell by specifically blocking ATGL.

So, why do hypoxic cancer cells try to block fat breakdown? One suggestion is that it protects them from by-products of fat metabolism – reactive oxygen species (ROS) – which cause cell stress and ultimately cell death. Indeed, the team's next experiments showed that in cells without HIG2, low-oxygen conditions caused excessive production of ROS – an increase of nearly 250%. In mice with tumours, deleting HIG2 caused a profound delay in tumour growth compared to mice with functioning HIG2.

"We have found a crucial survival mechanism that cancer cells use when under pressure from low-oxygen levels," concludes senior author Jun Liu, MD, Ph.D., Associate Professor of Biochemistry and Molecular Biology at Mayo Clinic's Arizona campus. "Our results justify further investigation of the HIG2–ATGL interaction as a prime therapeutic strategy for treating a broad range of aggressive cancers."

More information: Xiaodong Zhang et al, Inhibition of intracellular

lipolysis promotes human cancer cell adaptation to hypoxia, *eLife* (2017). DOI: 10.7554/eLife.31132