Overstuffed cancer cells may have an Achilles' heel

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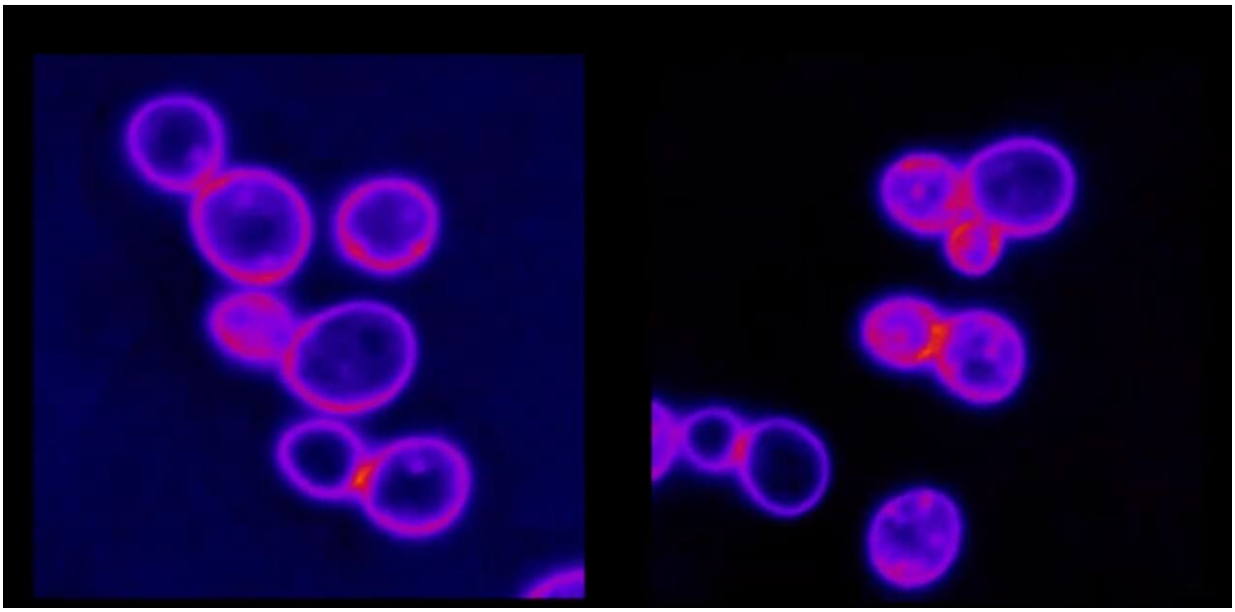

Aneuploid yeast cells on the left have difficulty drawing in fluorescent molecules. Whereas, the normal yeast cells on the right are able to rapidly draw them in. Credit: Rong Li and Hung-Ji Tsai

In a study using yeast cells and data from cancer cell lines, Johns Hopkins University scientists report they have found a potential weak spot among cancer cells that have extra sets of chromosomes, the structures that carry genetic material. The vulnerability, they say, is rooted in a common feature among cancer cells—their high intracellular protein concentrations—that make them appear bloated and overstuffed,

and which could be used as possible new targets for cancer treatments.

"Scientists are now thinking more about targeting the biophysical properties of cancer cells to make them self-destruct," says Rong Li, Ph.D., Bloomberg Distinguished Professor of Cell biology and Oncology at the Johns Hopkins University School of Medicine and of Chemical and Biomolecular Engineering at the Johns Hopkins Whiting School of Engineering.

Further research is planned to confirm the findings in animal and human cancer cells, says Li.

A report on the research, led by Li, is published in the June 6 issue of *Nature*.

The new experiments focused on a chromosome number abnormality known as aneuploidy. Normal human cells, for example, have a balanced number of chromosomes: 46 in all, or 23 pairs of different chromosomes. A cell with chromosomes that have extra or fewer copies is called aneuploid. Li says, "aneuploidy is the #1 hallmark of cancer," and is found in more than 90% of solid tumor cancer types.

When cells gain chromosomes, Li says, they also get an extra set of genes that produce more than the normal amount of protein that a cell makes. This excess can give cells growth abilities they normally wouldn't have, sometimes allowing them to overgrow and develop into a tumor.

Because aneuploid cells have unbalanced protein production, they have too many free-floating proteins that are not organized into a complex. This increases the concentration inside of the cell compared to outside. To compensate for the increased concentration, the cells draw in water, a phenomenon that leads to hypo-osmotic stress.

"Aneuploid cells tend to be bigger and more swollen than cells with a balanced number of chromosomes," says Li.

Li, who is a member of the Johns Hopkins Kimmel Cancer Center, says she and her team set out to see if there was a common Achilles' heel among aneuploid cancer cells, one that would make a powerful strategic target for cancer treatment.

For the study, which took nearly five years to complete, Li and her colleagues, including first author and Johns Hopkins postdoctoral fellow Hung-Ji Tsai, Ph.D., looked at yeast cells, which have 16 chromosomes. In stressful environments, such as those with cold temperatures or inadequate nutrients, yeast cells adapt by altering the number of chromosomes, which allows them to survive better due to changes in the relative amounts of various proteins.

Li and Tsai looked at gene expression levels of thousands of aneuploid yeast cells compared with normal ones. Specifically, the scientists looked for gene expression changes that were shared among the aneuploid cells despite their differences in chromosome copy number. Among the aneuploid cells, the scientists found that gene expression was altered in about 4% of the genome compared with normal cells.

Next, the scientists compared the aneuploidy-associated gene expression with information from a database at Stanford University that contains changes in gene expression among normal yeast cells exposed to different stressful environments. They found that both the aneuploid cells and normal cells under hypo-osmotic stress share certain gene expression characteristics. They also share the problem of being bloated, affecting their ability to internalize proteins located on the cell membrane that regulate nutrient uptake.

Li's team continued its work to see if it could exploit aneuploid cells'

vulnerability in properly controlling the intake of nutrients. They screened the yeast genome and found a molecular pathway involving two proteins called ART1 and Rsp5 that regulate the cells' ability to draw in nutrients such as glucose and amino acids. When the scientists inactivated these proteins in the aneuploid yeast cells, they lacked the proper intracellular nutrient levels and were less able to grow.

The human equivalent of the molecular pathway involves proteins called arrestins and Nedd4.

"It's possible that we could find a treatment that targets this or another pathway that exploits the vulnerability common to aneuploid cancer cells ," says Li.

More information: Hung-Ji Tsai et al. Hypo-osmotic-like stress underlies general cellular defects of aneuploidy, *Nature* (2019). DOI: 10.1038/s41586-019-1187-2

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