Researchers identify genetic dependencies in tumors that have undergone whole genome doubling

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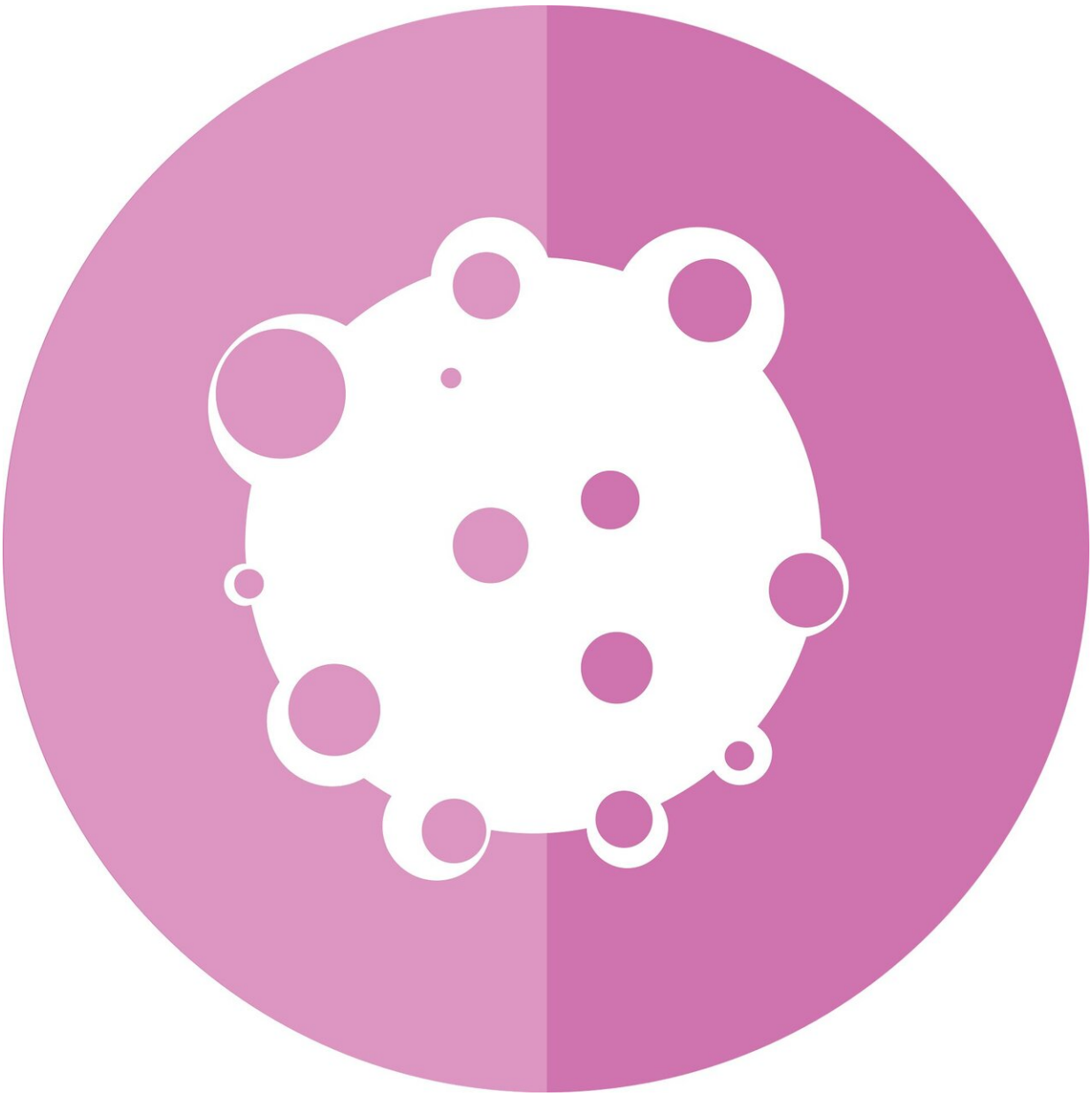

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Researchers from Boston University School of Medicine (BUSM) have identified proteins that are essential for the viability of whole genome doubled tumor cells, yet non-essential to normal cells that comprise the majority of human tissue.

"Exploiting these vulnerabilities represents a highly significant and currently untapped opportunity for therapeutic intervention, particularly because whole genome doubling is a distinguishing characteristic of many tumor types," said corresponding author Neil J. Ganem, Ph.D., associate professor of pharmacology and medicine, section of hematology and medical oncology, at Boston University School of Medicine (BUSM).

The vast majority of human cells are diploid, meaning that they possess two copies of each chromosome (one from each parent). Numerous cell cycle controls exist to ensure that this state is maintained across successive cell divisions. Despite these controls, errors can occur that result in a whole genome doubling (WGD), in which a diploid cell transitions to a tetraploid state (where cells have four copies of each chromosome, instead of two). WGD cells are oncogenic, and their contribution to tumor development is quite significant: Computational analyses from the Ganem lab have revealed that approximately 35 percent of all solid tumors arise from cells that have experienced a WGD event.

While WGD confers traits that favor tumor formation, it also imposes numerous physiological stresses upon cells. This led Ganem and his

colleagues to hypothesize that WGD tumor cells must acquire specific genetic alterations that enable them to tolerate the numerous defects imparted by a doubled cellular and genomic content, and that these tumor cells may therefore possess specific dependencies not present in normal diploid cells.

Using sequencing data from approximately 10,000 primary human cancer samples and data from nearly 600 cancer cell lines, the researchers found that WGD gives rise to common genetic traits that are accompanied by unique vulnerabilities. They identified several genes that are specifically required for the viability of WGD cells, including KIF18A, which is non-essential in normal diploid cells but becomes completely essential in WGD cancer cells.

"Currently, WGD status of cancer patients is not reported clinically because it does not inform treatment options. However, our study suggests that WGD cancer cells, based on their unique cellular physiology, may be specifically sensitive to a whole new variety of therapeutics. These findings may therefore validate the inclusion of WGD status as a new variable in future personalized medicine options," explained Ryan Quinton, an MD/Ph.D. student in Ganem's lab who was the lead author on the study.

These findings appear online in *Nature*.

More information: Ryan J. Quinton et al, Whole-genome doubling confers unique genetic vulnerabilities on tumour cells, *Nature* (2021). DOI: 10.1038/s41586-020-03133-3

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