Study suggests chromosomal errors may hinder some aggressive tumors

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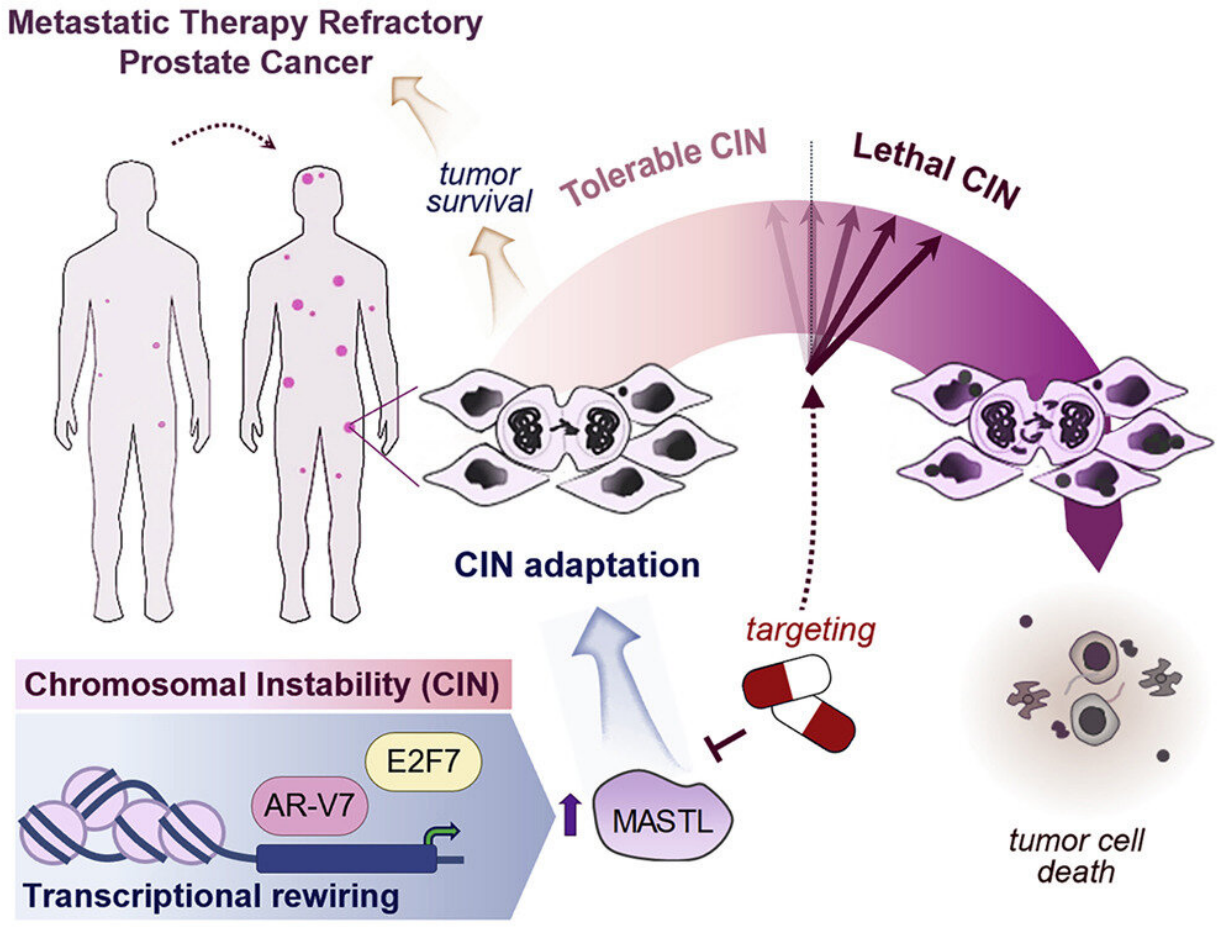

Graphical abstract. Credit: *Cell Reports Medicine* (2023). DOI: 10.1016/j.xcrm.2023.100937

Chromosomal errors are a hallmark of cancer cells. Defects in the genome derived from the incorrect separation of chromosomes (and the DNA packed within) in each division of cells drive tumor growth and resistance to therapy.

However, the opposite is also true, as very high levels of this persistent, chaotic genome scrambling, called chromosomal instability, is detrimental for tumors. Consequently, cancer cells must restrain these errors to survive.

In a research study published recently in *Cell Reports Medicine*, Mayo Clinic molecular and cancer cell biologist Veronica Rodriguez-Bravo, Ph.D., and her team identified a "brake" used by tumor cells that enables them to survive high chromosomal instability and become more aggressive. The researchers also discovered that therapy-resistant prostate cancer tumors display the highest chromosomal instability compared to other tumor types. If future therapies were developed to continue the instability—i.e., thwart the "braking" effect, this may potentially stop the cancer cells from growing and surviving.

"This study challenges further the dogma that chromosomal errors are mainly tumor-promoting and proposes that the errors can actually be the Achilles' heel of aggressive tumors like those in metastatic prostate cancer," Dr. Rodriguez-Bravo says.

"Typically, these tumors are considered 'invincible'; thus, finding they are selectively sensitive to drugs that lead to even higher chromosomal aberrations in tumor cells was very important. For many years,

chromosomal errors were thought to be mainly tumor-promoting because they are associated with aggressive tumors' progression."

Investigators studied experimental models such as prostate cancer cells and patient-derived preclinical models, combined with analysis of patient data. The team found that prostate cancer cells with a high level of chromosomal instability activate specific genes that stop the cells from acquiring more chromosome errors, ensuring the cancer cells survive and continue to promote tumor growth. Thus, aggressive, therapy-resistant tumors can avoid reaching catastrophic genome error levels that would kill them.

More information: Brittiny Dhital et al, Harnessing transcriptionally driven chromosomal instability adaptation to target therapy-refractory lethal prostate cancer, *Cell Reports Medicine* (2023). DOI: 10.1016/j.xcrm.2023.100937

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