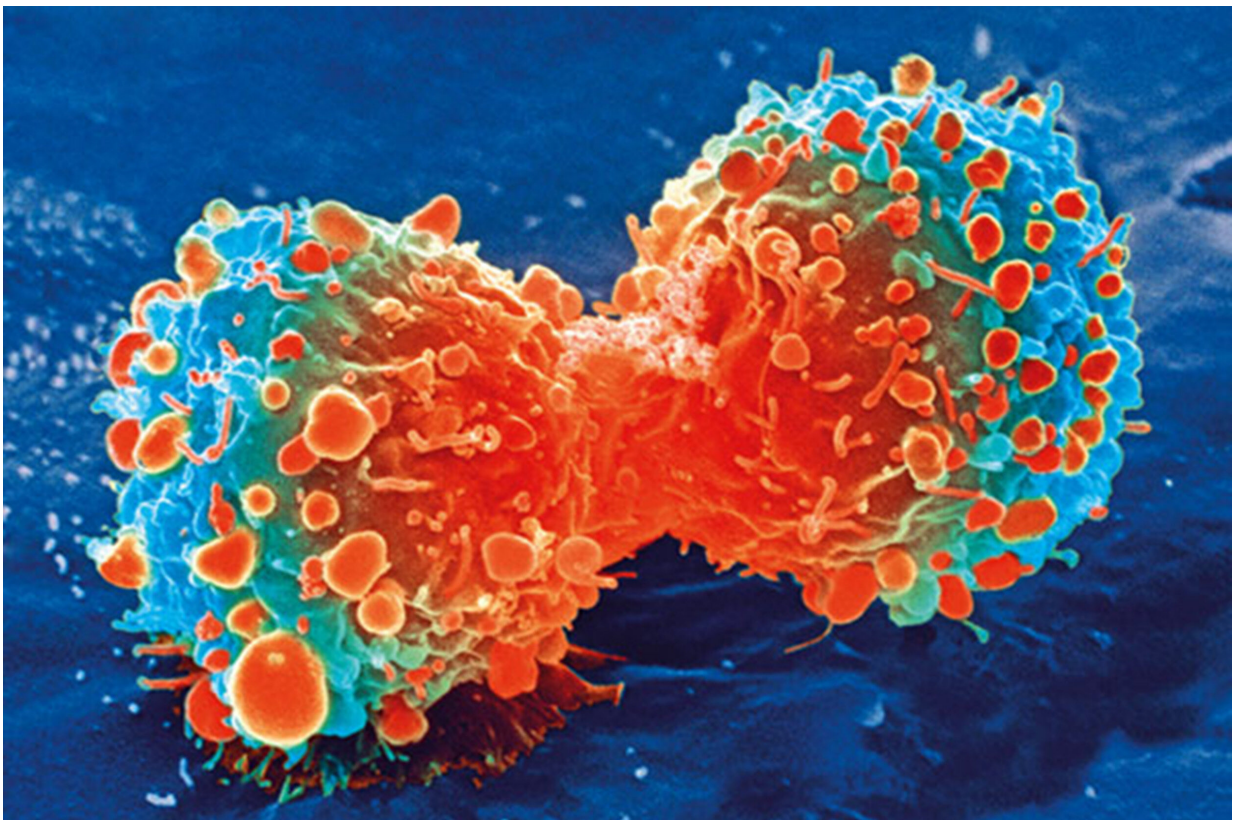
Thermal stress elicits genomic changes that can make cancer cells resistant to chemotherapy

February 22 2019



Cancer cell during cell division. Credit: National Institutes of Health

Harsh treatments that fail to eliminate tumors can make them more resilient, a new A*STAR study finds. Elevated temperature, nutrient

deprivation, or other environmental stressors can cause cancer cells to acquire large-scale genomic changes, some of which make them resistant to the drugs commonly used in cancer care.

This finding offers a warning about anti-cancer treatments that eliminate tumors by applying maximal therapeutic pressure. "While harsh treatments are needed to kill cancer cells, our research suggests that they might act as a double-edged sword," says Giulia Rancati, a cell and evolutionary biologist at the A*STAR Institute of Medical Biology, who led the study.

Therapy regimens will have to be evaluated holistically, Rancati explains. Oncologists will need to take the size of the tumor, its level of aggressiveness, and other characteristics into consideration when designing treatment protocols.

Chromosomal abnormalities are a hallmark of most tumors, and genetic mutations can lead cancer cells to develop growth differences, survival advantages, or increased resistance to therapeutic pressures.

Working with human colon cancer cell lines, Rancati and her colleagues induced changes in chromosomal numbers in three different ways. The investigators blasted the cells with an extra 5°C of heat (compared with normal culture conditions) for a few hours every day. They starved the cells (of fetal cow serum) for days, an essential supplement for cellular growth. And they kept the cells at oxygen concentrations well below healthy levels.

All three culture conditions elicited strong stress responses in the cells, which led to defects in cell division. Consequently, when a cancer cell split in two, pairs of matching chromosomes failed to sort properly.

This problem was most pronounced in cells exposed to heat stress, so the

researchers conducted more experiments on that particular environmental pressure. They found that the shock of the added temperature impaired a molecular safeguard that normally ensures faithful chromosome transmission during cell division. As a result, cells failed to separate, despite having already doubled their genomes, generating a "super-cell" with twice the usual number of chromosomes—a condition known as tetraploidy.

The A*STAR team, which included Zhihao Tan from the Genome Institute of Singapore, and Norman Pavelka from the Singapore Immunology Network, grew both the tetraploid "super-cells" and the normal diploid cells in lab dishes containing various chemotherapy medications. Compared to the cells with the usual chromosome count, the super-cells—which contain more DNA with which to resist the therapeutic onslaught—persisted at greater concentrations of doxorubicin, and in the presence of drugs, such as bleomycin and daunorubicin, that would otherwise have proven deadly.

Many cancer clinics around the world perform a kind of 'thermal therapy' in which heat is applied locally, regionally or to a patient's entire body to enhance the effects of radiation or drug treatment. Studies have shown that many types of cancer—sarcoma, melanoma, and cancers of brain, lung, breast, liver and other organs—respond better when heat is combined with other treatments.

However, the data from the new study suggest that thermal therapy can backfire for patients under certain circumstances. Because of the heat stress, Rancati says, "there might be cells that are able to survive the treatment, change their genome, and become resistant."

One solution may be to add a drug that blocks cell division to the mix to negate the potential for genome doubling presented by the thermal pressure. Ultimately, however, heat regimens will have to be re-

evaluated in light of the risk revealed by the A*STAR scientists.

Rancati next hopes to confirm the findings from her cellular investigations in mouse models of cancer.

More information: Zhihao Tan et al. Environmental stresses induce karyotypic instability in colorectal cancer cells, *Molecular Biology of the Cell* (2018). DOI: 10.1091/mbc.E18-10-0626

Provided by Agency for Science, Technology and Research (A*STAR), Singapore