Biologists report on the long-term effects of heat stress on cells

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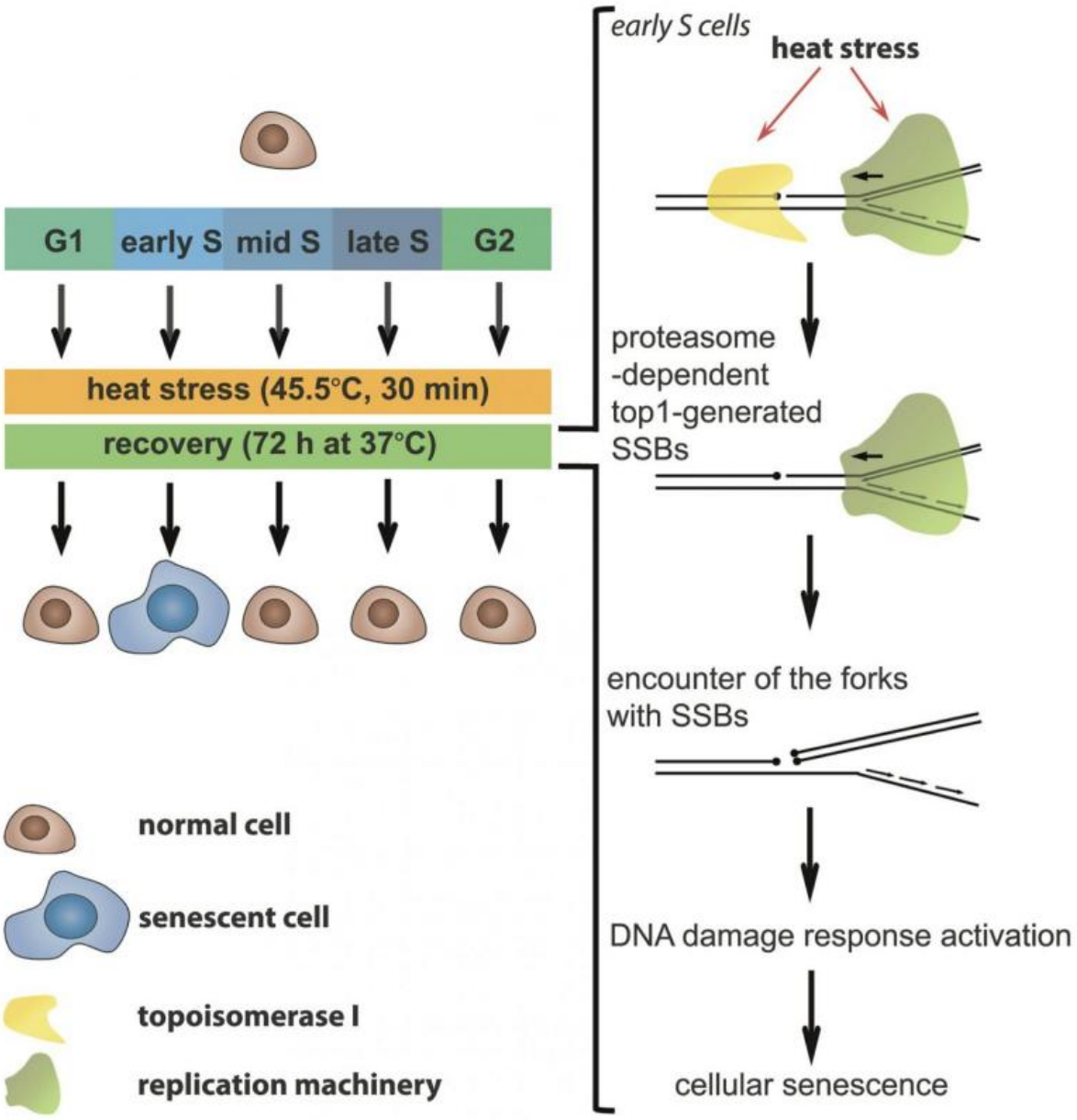

A process of cell senescence is set in the early S-phase, when a topoisomerase-I collides a replication fork and a double-strand break appears. Credit: Sergey Razin (NAR paper)

Heat shock (or stress) is a well-known factor of cell stress, though its delayed effects remain largely unknown. According to two articles by Russian scientists —a 2015 article in *Nucleic Acids Research* and a February article in *Cell Cycle*—heat shock mostly influences cells at an early synthetic phase, and not only temporarily stops DNA replication, but also causes some more serious consequences. According to one of the authors, Sergey Razin, head of the molecular biology department of Lomonosov Moscow State University, the results of the research may lead to new methods for curing cancer.

When a cell breaks forks

Cellular stress is caused by heat, cold, lack of oxygen, changes in acidity level, inflammation, infection or toxins, irradiation with x-rays or ultraviolet light. Biologist Sergey Razin says, "We have demonstrated that acute heat stress triggers development of cellular senescence in normal and cancerous cells that are at an early S-phase of a cell cycle. We identified the mechanism by which heat stress induces cellular senescence. The reason for heat stress-induced senescence is persistent DNA damage response connected with the formation of difficult-to-repair, double-stranded DNA breaks."

Using a wide range of methods, Russian scientists from MSU and Institute of Gene Biology, RAS, showed that a cell under stress is able to "break forks." This describes the structures in double-stranded DNA

when the double helix is split so that each strand could serve as a template for the synthesis of a new DNA chain in cellular reproduction. This duplication of DNA is based on a complementary principle stating that each nucleotide—a 'letter' of a DNA being synthesized— is selected based on the type of nucleodide present in this position in the template chain.

The researchers discovered that heat stress suppresses the activity of topoisomerase I, which relaxes DNA during replication by cutting one of the two strands. That leads to breaks in one strand, and when a replication fork reaches that spot, the other strand is also broken. When both strands are damaged, DNA is extremely difficult to repair.

One more exciting outcomes of this study, according to Razin, is "a demonstration that genetically identical cells may differ dramatically both in resistance to exogenous stress factors and a type reaction to various stresses." Just as stress influences a person differently across a lifetime, cellular stress depends on the stage of the cell cycle, another subject addressed in the study.

Childhood, adolescence, youth, mitosis

The lifetime of each somatic cell depends on its peculiarities—erythrocytes (biconcave red blood cells) live about 120 days, and epithelial cells lining the inside of the intestine about one to two days. Neurons and striated muscle tissue cells live just as long as the organism. Fast-living cells are constantly dividing to provide a sufficient replacements, while long-living cells almost never do.

With all that diversity, somatic cells may be said to have four cell cylce phases: G1, S, G2 and mitosis, a division phase that results in building two identical daughter cells inheriting a chromatid—one half of a mother's chromosome. During the G1, pre-synthetic phase, cell growth

occurs, and the cell is prepared for DNA doubling. Having received half of a chromosome, a cell needs to complete it in order to pass it to the next generation. This doubling synthetic phase happens during the S-phase. Accuracy in copying genetic information is under the strict control of the p53 protein. When a DNA strand is damaged, it boosts production of the p21 protein, which is connected to a complex of cyclin and cyclin-dependent kinases, responsible for initiating the next stage of the cycle. This delays the start of the S-phase, giving repair enzymes time to fix the damage. Then the G2 phase occurs, during which the cell grows and prepares itself for future division. At this stage, DNA is again subject to a mandatory inspection, and then mitosis begins. After mitosis, each of the newborn cells begins the G1 stage, and the cycle repeats.

Some cells leave a row of divisions, hovering in the G0 phase, which, in a first approximation, is the G1 phase extended to an eternity; for the remaining cells, the cycle is also finite—after approximately 52 divisions, the cell ages, stops mitosis, and eventually dies. But when DNA in a cell is damaged so much that it is hard to repair, the cell cycle is terminated to avoid copying damaged genetic code, thereby creating generations of mutants, which leads to inflammation and the development of cancer tumors.

"Based on cell reaction to heat stress, we formulated a model of cell senescence induction, which holds for many DNA-damaging agents. According to this model, any single- or double-stranded break happening at an early S-phase may initiate the cell senescence program," says Razin.

The value of this research is ambiguous. On the one hand, scientists aspire to prevent the aging of normal cells to help them resist stress and function as long as possible. On the other hand, the controlled start of cellular senescence helps those cells deviating from the genetic program

to die before becoming cancerous. That is why forcing defective cells to stop dividing and multiplying is vital for curing oncologic diseases.

"Disclosure of the mechanisms of cellular senescence induced by a mild genotoxic (DNA-damaging) stress appears to be important both for understanding the reasons and mechanisms of aging, and a better understanding of cell response variability to exogenous and endogenous stress factors. This research also casts light on multiple previously unattended effects of DNA-damaging agents—for instance, camptothecin—which are often used in cancer therapy. Theoretically, the results of the study may form the basis for an optimization of existing protocols of simultaneous application of hyperthermia and chemotherapeutic agents for curing oncologic diseases," Razin concludes.

More information: Artem K. Velichko et al. Mechanism of heat stress-induced cellular senescence elucidates the exclusive vulnerability of early S-phase cells to mild genotoxic stress, *Nucleic Acids Research* (2015). DOI: 10.1093/nar/gkv573

Nadezhda V. Petrova et al. Early S-phase cell hypersensitivity to heat stress, *Cell Cycle* (2015). DOI: 10.1080/15384101.2015.1127477

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