When the Cell's Copy Machine Jams: Scientists Reveal a Hidden Source of DNA Damage

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Researchers from the Institute of Molecular Genetics of the Czech Academy of Sciences in Prague in collaboration with colleagues from the University of Zurich and the University of Bern, have uncovered a new explanation for why cancer cells accumulate DNA damage and why their chromosomes so often become unstable. Published in Nature Communications, the study reveals how everyday problems arising during DNA copying can quietly build up over time and undermine genome integrity.

One of cancer's defining features is genomic instability — chromosomes that are broken, rearranged, or unevenly distributed between daughter cells. This instability fuels tumor evolution, drug resistance, and disease progression. Yet it rarely arises from a single dramatic event. Instead, this research shows that chromosomal chaos often develops gradually, driven by repeated disruptions during routine DNA duplication. By identifying where and how cells lose control, this basic research exposes vulnerabilities in cancer cells and highlights cellular repair pathways that may one day inspire new therapeutic strategies.

Every time a cell divides, it must accurately copy its entire DNA — a task comparable to duplicating an enormous instruction manual, letter by letter. At the same time, cells are also using those instructions to produce RNA, short working copies of genes that guide protein production. Under healthy conditions, DNA copying and RNA production are carefully coordinated so they do not interfere with one another.

Cancer-causing genes disrupt this coordination. A useful way to visualize the problem is a copy machine in constant operation. The machine is designed for smooth, continuous copying — but if loose sheets or fragments accumulate inside while it is still running, paper jams quickly form. The research team discovered that a similar problem occurs inside cells.

During active DNA copying, newly made RNA can sometimes bind back onto the DNA, forming abnormal hybrid structures known as R-loops. These structures are not inherently harmful, but when they accumulate, they obstruct the DNA-copying machinery. The study shows that two major cancer-associated drivers — oncogenic RAS and overexpression of Cyclin E1 — substantially increase R-loop formation. Although they act through different biological pathways, both generate the same result: frequent stalling of DNA replication at these molecular obstacles.

The researchers found that RAS increases chemical stress inside cells by elevating reactive oxygen species, which alter the behavior of the DNA-copying machinery itself. Cyclin E1, in contrast, pushes

cells prematurely into division, increasing collisions between DNA copying and transcription. Despite these differences, both lead to recurring replication stress.

Cells attempt to manage these problems through built-in safety mechanisms. When DNA copying stalls, the replication machinery can temporarily reverse direction, a process known as fork reversal, allowing the cell time to stabilize the situation. While protective in the short term, the study uncovered an important trade-off: if reversed replication structures persist, they interfere with the precise separation of chromosomes during cell division. In other words, a response that initially protects DNA can later contribute to chromosome breakage, rearrangements, and mis-segregation — hallmarks of cancer cells.

Importantly, the team also identified an alternative recovery pathway. By activating a restart mechanism involving the enzymes MUS81 and PRIMPOL, cells can bypass stalled regions and resume DNA copying. Though less refined, this strategy reduces persistent replication blockages and markedly improves chromosome segregation during division. In practical terms, clearing certain jams promptly may be safer than repeatedly reversing and risking long-term instability.

This multidisciplinary research combined molecular biology, cancer genetics, and advanced imaging to illuminate how cells respond to chronic DNA copying stress. It underscores the power of fundamental research to reveal disease mechanisms that cannot be detected by studying tumors alone.

Cancer does not arise only from damaged genes, but from failures in how cells manage routine stress during DNA copying. By uncovering how these invisible disruptions accumulate over time, this study demonstrates why basic research is essential for understanding — and eventually intercepting — disease at its earliest molecular stages.

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