

Cells do not repair damage to DNA during mitosis because telomeres could fuse together

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When imposing repair on broken DNA strands during mitosis, some telomeres are seen to fuse together (one dot). Credit: A. Orthwein/Durocher Lab

Throughout a cell's life, corrective mechanisms act to repair DNA strand breaks. The exception is during the critical moment of cell division, when chromosomes are most vulnerable. Toronto researchers found out why DNA repair shuts down during mitosis.



The paradox of a cell that shuts down its DNA repair processes during cell division has been solved, according to research published in Science on March 20, 2014. The problem had eluded science for six decades.

"We now know why a crucial DNA-repair process shuts down just when the cell starts to divide into two daughter cells," says Dr. Daniel Durocher, a Senior Investigator at the Lunenfeld-Tanenbaum Research Institute at Mount Sinai Hospital in Toronto, Canada.

Throughout most of a cell's life, corrective mechanisms are nearly always acting to repair DNA strand breaks quickly and accurately. "DNA repair helps thwart cancer and keep the cell in top shape – it is usually all in a day's work within each cell," Dr. Durocher adds.

Paradoxically, the exception is at the very moment when chromosomes are most vulnerable, when they physically separate into two cells at cell division (mitosis).

Telomeres fuse if repair is forced

"A cell replicating its DNA is like making a back-up copy of your hard drive," suggests lead author Dr. Alexandre Orthwein. "You want the copy to be exactly like the original, and you don't want any errors to creep in during the copying process." Dr. Orthwein is completing a postdoctoral fellowship in the Durocher lab.

Dr. Durocher and his team worked backwards. First, they determined how <u>repair proteins</u> failed to recognize and act on chromosome breaks during cell division. Next, they modified the repair proteins in order to impose DNA repair during mitosis, and watched what happened.

"We observed a very surprising effect," says Dr. Orthwein. Repairing the chromosome damage during cell division caused it to be defective. The



problem was traced to <u>telomeres</u>- structures found at the end of chromosomes that protect them from erosion- that began to fuse to each other when DNA repair was re-activated.

"In other words, at that moment of cell division, the cell miss-identified its own telomeres as damaged DNA, which it then 'repaired," Dr. Orthwein says.

This revealed telomeres as dangerous structures during mitosis, because the cells momentarily lost the ability to distinguish between damaged DNA strands and normal telomeres. "While we don't yet know why this happens, it's so remarkable that it tells us something fundamental about telomeres and cell division. This is forming the basis of our future work," Dr. Durocher explains.

The finding shows that cells have a difficult choice to make during this vulnerable period of cell division, adds Dr. Orthwein. "They take the drastic action of turning off DNA repair, a process that is usually highly beneficial, to prevent chromosomes from fusing with each other by mistake."

"We often assume that we know all the principles that guide basic processes like how <u>cells</u> divide," says Dr. Jim Woodgett, Director of the Lunenfeld-Tanenbaum Research Institute. "But there is still so much to discover and this is a wonderful example of how an old conundrum was resolved by asking the right questions."

Can this new knowledge be exploited therapeutically? Dr. Durocher adds that, "Some chemotherapy drugs such as paclitaxel work by stopping <u>cell</u> <u>division</u>. Theoretically, it may be possible to enhance the efficacy of these drugs based on our findings, but if so it's in the future."

More information: "Mitosis inhibits DNA double-strand break repair



to guard against telomere fusions" Science, 2014.

Provided by Lunenfeld-Tanenbaum Research Institute

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