Researchers clock DNA's recovery time after chemotherapy

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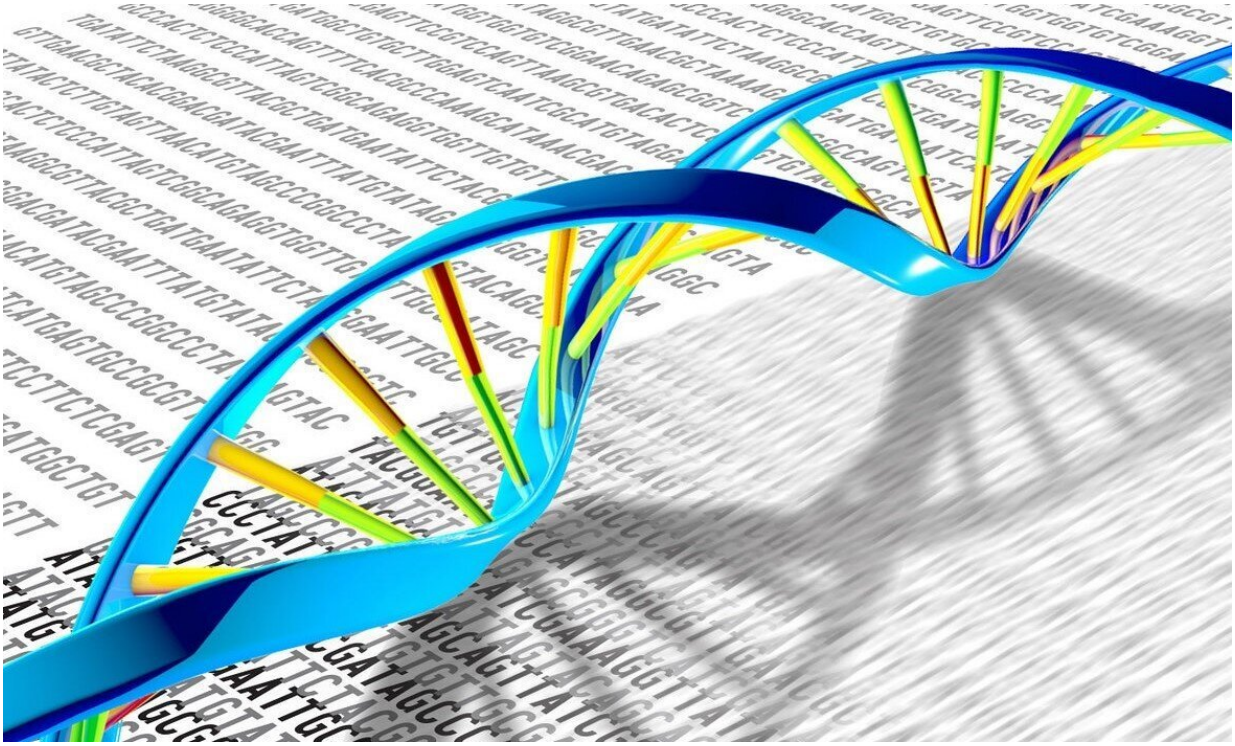

DNA, which has a double-helix structure, can have many genetic mutations and variations. Credit: NIH

In the time it takes for an Amazon Prime delivery to arrive, cells damaged by chemotherapy can almost completely fix their most important DNA. That is the case in the livers of mice at least, according to a new study.

A team of researchers led by Nobel laureate Aziz Sancar found that DNA damaged by the widely used chemotherapy drug cisplatin is mostly good as new in noncancerous tissue within two circadian cycles, or two days. The results published in the *Journal of Biological Chemistry* could inform the development of chronochemotherapies—strategies aimed at administering chemotherapy drugs at times that maximize tumor damage while minimizing side effects.

Cisplatin is a frontline drug for numerous cancers, but it often is accompanied by serious side effects including kidney, liver and peripheral nerve injury. Since cisplatin kills cells, cancerous or otherwise, by damaging their DNA, Sancar and his team aimed to uncover the pattern of DNA repair in healthy cells, which could reveal when it might be best to administer cisplatin. In normal cells, the circadian clock drives the rhythm of DNA repair, but this is not the case in tumors.

"Most cancers do not have a functional clock and so, basically any time that it's good for the normal tissue, you can hit the cancer," said Sancar, professor of biochemistry and biophysics at the University of North Carolina School of Medicine.

In an earlier study, Sancar's team provided a first look at DNA repair across the genome of whole animals (mice in this case), uncovering two mechanisms of circadian-controlled DNA repair.

They found that for some genes, transcription—during which damaged DNA is recognized and patched up—was rhythmic and controlled by the circadian clock. The pattern of transcription was specific to each gene, with repair peaking at different times of day. For the remaining DNA that was not transcribed, repair was less efficient but also clock-controlled, and maximum repair occurred between 4 p.m. and 6 p.m., Sancar said.

They examined DNA two hours after injecting cisplatin in this previous experiment, but in their new work in JBC, Sancar's team wanted to study the recovery of DNA following administration of cisplatin on a more clinically relevant time scale.

"We recapitulate what has been done in patients because in patients you give cisplatin (intravenously) at either weekly, 10-day or two-week intervals. So you give one dose and then let the patient recover for a week or so and then give the second dose. And so we wanted to know what happens over those long periods," Sancar said.

The team used a technique developed in their lab, known as XR-seq, to capture and sequence fragments of damaged DNA from mice injected with cisplatin. Over the course of 70 days, they produced maps displaying where and when DNA was fixed at the resolution of a single nucleotide.

They found that the DNA of transcribed genes was just about fully mended in two circadian cycles, Sancar said. Restoration of these genes composed the majority of repair during the first 48 hours but afterward, repair of nontranscribed DNA became dominant and proceeded for weeks.

The remaining damage in nontranscribed DNA is not harmful in normal cells that aren't replicating, Sancar said. But for cancer cells which divide uncontrollably, this damage could lead to cell death.

This new information about the timetable of DNA repair could eventually aid the design of successful chronochemotherapies, but before this information is considered in the clinic, further experiments are needed, Sancar said.

Sancar himself is already at work with oncologists, evaluating new

cisplatin regimens in mice implanted with human tumors to find a treatment that reduces toxicity in normal tissue while hitting cancer hard.

More information: Yanyan Yang et al, Long-term, genome-wide kinetic analysis of the effect of the circadian clock and transcription on the repair of cisplatin-DNA adducts in the mouse liver, *Journal of Biological Chemistry* (2019). DOI: 10.1074/jbc.RA119.009579