

By solving a mystery of gene repair, scientists uncover an exception to biology's rules

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Dale Ramsden, PhD. Credit: University of North Carolina at Chapel Hill School of Medicine

About 15 years ago, UNC Lineberger's Dale Ramsden, Ph.D., was looking through a textbook with one of his students when they stumbled upon a scientific mystery.

A small line in the book indicated that a protein that helps [repair](#) major breaks in our [genetic code](#) did so by adding DNA, or deoxyribonucleic acid, as expected. However, there were hints that it could also add RNA, or ribonucleic acid, at least in a test tube. It seemed unlikely that this

would occur during repair of DNA in living [cells](#), since RNA is normally used only as a messenger to carry information from the genetic code to make proteins.

"You would think they must only add DNA during repair of our genetic code, because that's the core of the central dogma of life; genetic information has to be DNA all the time," said Ramsden, who is a professor in the UNC School of Medicine Department of Biochemistry and Biophysics. "That's the way it's supposed to be. That's what we're taught in school."

Fast forward to today, as the Ramsden lab publishes a major study in the journal *Science* showing that in living cells, this protein, which is a type of genetic repair and replication tool called a polymerase, most often adds RNA when fixing major breaks in our DNA genetic code. Their research also revealed surprising insights into why RNA is used.

"It took us 15 years to get the systems we needed to actually ask the questions that would solve the mystery," Ramsden said.

To repair major DNA breaks, cells use 'get out of jail free' card

Ramsden is a scientist who studies DNA repair, a process cells undertake to fix breaks in our genetic code when it's been damaged by UV radiation, smoking, or accidentally during the day-to-day functions of a cell. DNA repair is essential, and when DNA repair is not functioning normally, it can lead to cancer. Ramsden is particularly interested in an approach to repair double-stranded breaks—which occur when both DNA strands are broken—called non-homologous end-joining.

"They're lethal to the cell, so you must repair them," Ramsden said.

"When (repair) goes bad, it generates the kinds of genetic re-arrangements and aberrations that are really a hallmark of most cancers."

Their latest study shows that to fix double-stranded breaks, the polymerase responsible for fixing DNA errors of double-stranded breaks essentially patches the fix by plugging the hole in the genetic code using an RNA.

They found that as much as 65 percent of repair done through the non-homologous end-joining process uses RNA.

Ramsden said using RNA is like a "get out of jail free card," allowing the cell to ignore other problems that would otherwise interfere with successful repair.

"What we show is that adding RNA helps to bypass other damage," Ramsden said. "They don't have to follow the strict rules of what they're normally used to requiring to repair a [break](#). The alternative would be not to repair it, which would lead to significantly more error."

Researchers evaluate applications for gene repair discovery

The study goes on to describe the repair process after RNA insertion, and the different ways this is used in cells, including in a process to create a diversity of white blood cells that can recognize many different invading pathogens – a process that requires double-stranded in our genetic [code](#).

Ramsden and his colleagues were able to make this finding because of several technological advances, including the ability to visualize the repair process very quickly in the short amount of time before the RNA

was replaced with DNA in the repair process.

"We can track the repair reaction almost in real time as it happens in the cell," Ramsden said.

They believe their findings have a number of applications, including a new way to sensitize cancer cells to DNA damage through radiation therapy by preventing this type of repair. Shutting down the repair pathway by inserting a compound other than RNA into the break would cause cancerous cells damaged by radiation therapy to die.

Ramsden said this was not only a major discovery for his career, but it also was the first time his research was directly relevant to what his daughter was learning in school, in this case, 10th grade biology.

"I was going, 'have I got a story for you,'" he said.

More information: John M. Pryor et al. Ribonucleotide incorporation enables repair of chromosome breaks by nonhomologous end joining, *Science* (2018). [DOI: 10.1126/science.aat2477](https://doi.org/10.1126/science.aat2477)

Provided by University of North Carolina at Chapel Hill School of Medicine

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