'Junk' DNA could lead to cancer by stopping copying of DNA

July 19 2022

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Scientists have found that non-coding "junk" DNA, far from being harmless and inert, could potentially contribute to the development of cancer.

Their study has shown how non-coding DNA can get in the way of the replication and repair of our genome, potentially allowing mutations to

accumulate.

It has been previously found that non-coding or repetitive patterns of DNA—which make up around half of our genome—could disrupt the replication of the genome.

But until now scientists have not understood the underlying mechanism, or how it could contribute to cancer's development. In the new study, scientists at The Institute of Cancer Research, London, reconstituted the entire process of DNA replication in a test tube in order to understand it more completely.

The researchers were able to describe how repetitive patterns of DNA are copied during replication and how they are able to stall replication entirely—increasing the risk of errors that can be an early driver of cancer. This vital knowledge may eventually lead to better drugs and treatments.

The researchers believe the work could also help to improve the diagnosis and monitoring of some cancers, such as bowel cancer, where common errors in copying the repetitive sequences of DNA indicate whether cancer is progressing.

The study was published in *Nature Communications*.

Scientists at the ICR—a charity and research institute—found that when the DNA replication machinery encountered repetitive DNA, it was able to unwind the DNA strands, but it sometimes failed to copy the opposite DNA strand. This error could cause replication to stall, resulting in collapse of the replication machinery in a manner similar to that induced by DNA damage.

The findings lead scientists to believe that repetitive DNA sequences

could trigger a damage response signal indicating that errors in DNA replication have occurred and require repair.

DNA damage and ensuing genome instability are known to promote cancer formation and progression, so the research strengthens the link between junk DNA and cancer.

It was scientists at the ICR who, in the 1960s, provided the first conclusive evidence that DNA damage is the fundamental cause of cancer. In the early 2000s, ICR researchers then showed that drugs called PARP inhibitors could be genetically targeted against cancers with DNA repair mutations.

Our researchers now hope that improved understanding of DNA replication, and how it can go wrong, might lead to new ways of treating the disease.

Study leader Dr. Gideon Coster, Team Leader in Genome Replication at The Institute of Cancer Research, London, says that they "wanted to understand why it seems more difficult for cells to copy repetitive DNA sequences than other parts of the genome. Our study suggests that so-called junk DNA is actually playing an important and potentially damaging role in cells, by blocking DNA replication and potentially opening the door to cancerous mutations."

"We now believe that repetitive DNA sequences trigger a response that is very similar to the one induced by DNA damage, which we know can lead to cancer. Our study therefore fundamentally advances our understanding of cancer, and I'm hopeful it will help us come up with new treatments in the future."

Professor Kristian Helin, Chief Executive of The Institute of Cancer Research, London, says that "this study helps to unravel the puzzle of

junk DNA—showing how these repetitive sequences can block DNA replication and repair. It's possible that this mechanism could play a role in the development of cancer as a cause of genetic instability—especially as cancer cells start dividing more quickly and so place the process of DNA replication under more stress."

"Understanding the mechanisms underlying genetic mutation and instability is critical if we are to find innovative new ways to treat cancer that exploit fundamental weaknesses in cancer cells."

More information: The mechanism of replication stalling and recovery within repetitive DNA, *Nature Communications* (2022). DOI: 10.1038/s41467-022-31657-x

Provided by Institute of Cancer Research

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