Study reveals RNA's role in regulating gene expression in cancer cells

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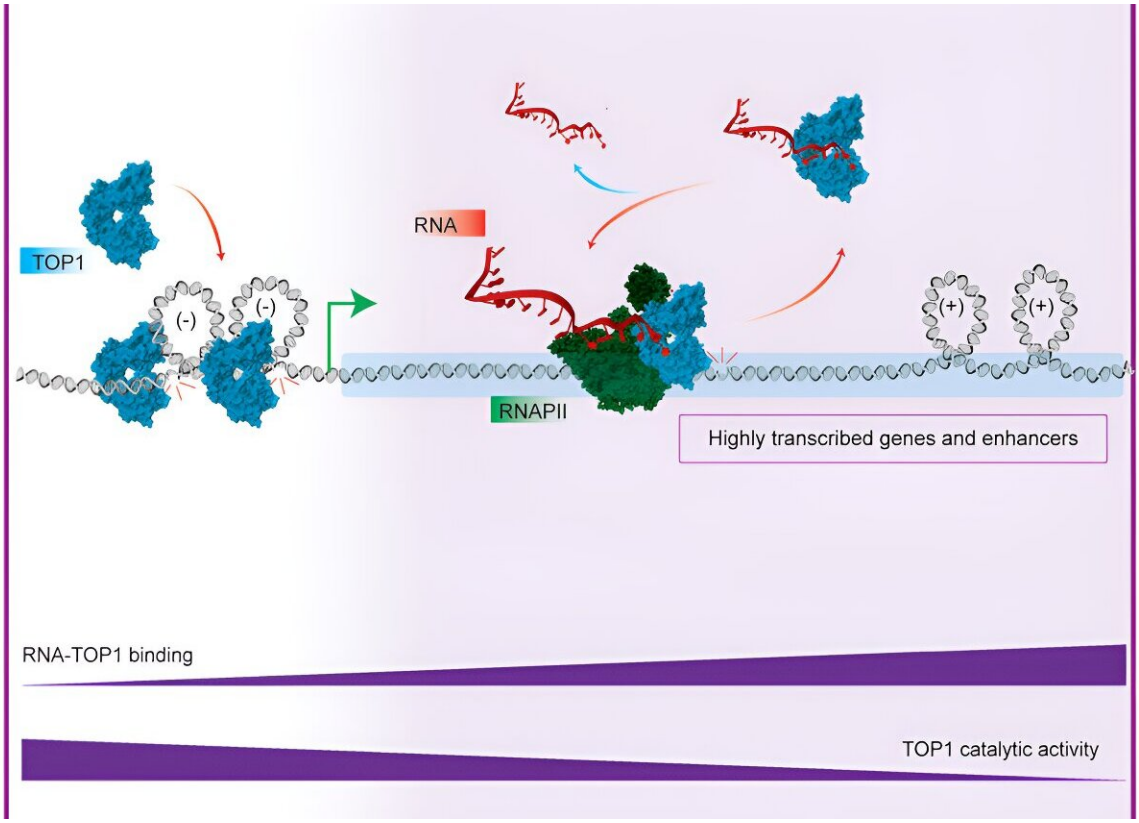

Credit: *Molecular Cell* (2024). DOI: 10.1016/j.molcel.2024.07.032

Scientists have discovered how interactions between RNA and the TOP1 essential enzyme, which is overexpressed in many human cancers, regulate DNA during transcription and may inform the creation of new

cancer therapies, according to a Northwestern Medicine study published in *Molecular Cell*.

"This study offers new mechanistic insights that could pave the way for developing novel chemotherapeutics by targeting the RNA binding interface with small compounds. Our findings reveal that inhibiting RNA binding of TOP1 may work similarly to well-known TOP1 inhibitors like camptothecin by increasing TOP1 catalytic complexes on DNA.

"This approach could induce genomic instability and potentially enhance our ability to kill cancer cells," said Shannon Lauberth, Ph.D., associate professor of Biochemistry and Molecular Genetics and senior author of the study.

"By developing drugs that can precisely control the binding and release of RNAs bound by TOP1, we may enhance the efficacy of existing cancer therapies but also make significant strides toward the development of new therapeutics," said Kouki Abe, Ph.D., a postdoctoral fellow in the Lauberth laboratory and co-first author of the study.

Topoisomerase I (TOP1) is an enzyme known for its role in preventing genomic instability by alleviating torsional strain in DNA by introducing transient single-strand breaks. According to Lauberth, this process of DNA relaxation prevents the accumulation of supercoiling and torsional stress that could otherwise lead to DNA damage and instability.

"If this process doesn't occur, transcription can be hindered, leading to double-strand DNA breaks and genomic instability. This can cause the cell to die and trigger apoptosis," said Lauberth, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

In cancer cells, DNA transcription is often elevated, necessitating increased levels of TOP1 activity to relax the DNA and maintain proper gene expression, but the underlying mechanisms that regulate TOP1 activity have remained unclear.

Using a combination of sequencing techniques and in vitro RNA binding assays, the investigators discovered that TOP1 binds to RNA and that most of these RNAs are mRNAs, which carry the genetic information required for protein synthesis.

Next, the investigators aimed to better understand why TOP1 binds to RNA in relation to its essential role in relaxing DNA. Using DNA supercoiling experiments, single molecule magnetic tweezer assays, and advanced sequencing methods, the investigators examined TOP1 catalytic activity and how it supports interactions with both DNA and RNA.

They discovered that RNA opposes TOP1 activity and, importantly, as RNA polymerase II—a multiprotein complex that transcribes DNA into mRNA—activated the transcription process.

"Our study uncovers a unique mechanism in which RNA modulates TOP1-mediated DNA relaxation, thereby playing a crucial role in regulating transcription. By identifying TOP1 as an RNA-binding protein, this research provides new insights into the interplay between RNA and DNA during transcription," says Mannan Bhola, Ph.D., a data analyst in the Lauberth laboratory and co-first author of the study.

More information: Mannan Bhola et al, RNA Interacts with Topoisomerase I to Adjust DNA Topology, *Molecular Cell* (2024). DOI: 10.1016/j.molcel.2024.07.032. www.cell.com/molecular-cell/fu … 1097-2765(24)00630-0

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