'Activating' RNA takes DNA on a loop through time and space

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Long segments of RNA—encoded in our DNA but not translated into protein—are key to physically manipulating DNA in order to activate certain genes, say researchers at The Wistar Institute. These non-coding RNA-activators (ncRNA-a) have a crucial role in turning genes on and off during early embryonic development, researchers say, and have also been connected with diseases, including some cancers, in adults.

In an online article of the journal *Nature*, a team of scientists led by Wistar's Ramin Shiekhattar, Ph.D., detail the mechanism by which long non-coding RNA-activators promote gene expression. They show how these RNA molecules help proteins in the cell to create a loop of DNA in order to open up genes for transcription. Their experiments have also described how particular ncRNA-a molecules are related to FG syndrome, a genetic disease linked to severe neurological and physical deficits. "These ncRNA-activators can activate specific genes by working with large protein complexes, filling in a big piece of the puzzle," said Shiekhattar, Herbert Kean, M.D., Family Professor and senior author of the study. "Our DNA encodes thousands of these ncRNA-activators, each with a role in timing the expression of a specific gene. As we learn more about non-coding RNA, I believe we will have a profoundly better understanding of how our genes function."

Their findings also provide a plausible mechanism of how locations along chromosomes, classically known as "enhancer" elements, can influence the expression ("reading") of genes located 5,000 to 100,000 base pairs ("letters") of DNA away. According to their findings, ncRNA-

a molecules bind to large protein complexes to form a loop of DNA, which then opens up the gene to the molecular machinery that transcribes DNA. "There is an abundance of evidence to indicate that enhancers are critical components of transcription during embryonic development and disease process," Shiekhattar said.

"Non-coding RNAs are probably one of the earliest molecules that determine spatial and temporal gene expression in a developing embryo," Shiekhattar said. "These enhancers can help turn genes on and off as a growing embryo would need, but as we have seen in other genetic mechanisms of embryonic development, they can lead to cancer if they are switched on inappropriately in adult cells."

In the classic "central dogma" of biology, chromosomal DNA is transcribed into RNA, which is then translated by the cell into proteins. In recent years, however, scientists have found that not all transcribed RNA molecules become translated into proteins. In fact, studies have shown that large portions of the genome are transcribed into RNA that serve tasks other than functioning as blueprints for proteins. In 2010, the Shiekhattar lab first published the discovery of these ncRNA enhancer molecules in the journal *Cell* (2010 Oct 1;143(1):46-58), and theorized on their role as "enhancers" of gene expression. Since then, laboratories around the world have published and linked ncRNAs not only to transcriptional enhancers but also to certain diseases, including some cancers.

To discover how such enhancer-like RNAs function, the Shiekhatter laboratory deleted candidate molecules with known roles in activating gene expression, and assessed if they were related to RNA-dependent activation. They found that depleting components of the protein complex known as Mediator specifically and potently diminished the ability of ncRNA-a to start the process of transcribing a gene into RNA. Further, they found that these activating ncRNAs can attach to Mediator at

multiple locations within the Mediator protein complex, and Mediator itself can interact with the enhancer element site on DNA that encodes these activating ncRNAs. Their results also determined how mutations in a protein that makes up the Mediator complex, called MED12, drastically diminishes Mediator's ability to associate with activating ncRNAs.

Mutations in the MED12 protein are a marker for FG syndrome (also know as Opitz–Kaveggia syndrome), a rare genetic disorder that leads to abnormalities throughout the body and varying degrees of physical and neurological problems. "This clearly shows how activating ncRNAs can influence disease development, an idea that has been gaining evidence in the scientific literature," Shiekhattar said. To confirm that ncRNA-a works with Mediator to form a loop in DNA, the researchers used a technique called chromosome conformation capture (3C) to gain a better understanding of the three-dimensional structure of chromosomes. Their results show how Mediator gets a foothold of sorts on the portion of DNA that encodes the ncRNA-a, and twists the DNA to form a loop.

"The looping mechanism serves to physically bring together a distant enhancer element with the start site of the targeted gene, allowing Mediator to recruit the proteins responsible for reading the gene to the location," Shiekhattar said. "It is at least one answer to how these classical enhancer elements function while being physically distant from their target genes."

Provided by The Wistar Institute

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