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Invisible tails help cancerous mRNA evade the body's censors

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In innumerable spy movies, the hero or a villain imprints a key in clay in order to later make an exact copy. In the body, the clay is messenger RNA, or mRNA, which imprints a gene and transfers the plans to a ribosome, where the mRNA's code is manufactured into a protein – the shady shop where the clay imprint becomes a key.

It's the body's job to recognize and destroy cancerous clay molds in transit – any mRNA that codes for an oncogenic protein. Only, the body frequently fails and mRNA that should be killed is instead allowed to be turned into its cancer-causing protein product.

The National Cancer Institute identified the method by which cancerous mRNA evades the body's safeguards as one of the 24 most provocative questions in cancer science. And the NCI Provocative Questions Project has entrusted the search for an answer to David Bentley, PhD, investigator at the University of Colorado Cancer Center and professor in the Department of Molecular Biology at the CU School of Medicine.

"mRNAs have a long tail of residues that won't necessarily be expressed in the protein it codes for," Bentley says. "And it was realized that many of these tails, called poly(A) tails, are mislocalized in cancer cells."

So, what difference does it make if an mRNAs extra, unexpressed tail is missing or in the wrong place? Well, "When you cut off these untranslated sequences, you can end up with runaway mRNA – when it loses those important pieces at the end, it can escape from regulatory

mechanisms that can keep it under control."

The body looks for an mRNA's poly(A) tail as a signal to make a thorough examination. Without this tail, or with an unrecognizable tail, cancerous mRNAs evade scrutiny.

In addition, Bentley describes the length of an mRNA's poly(A) tail effecting its stability. A stable mRNA stays still near the ribosome and allows itself to be easily read and copied; an instable mRNA turns over rapidly and is less likely to be made into a protein. And a mRNA's poly(A) tail presents docking bays at which regulators of this stability can attach – proteins and microRNAs that land at poly(A) tails can hold an mRNA stable for expression or make it instable and unreadable.

These tails are not easy to see. In fact, they're virtually invisible to traditional cancer scientists who have been most concerned with exploring patients' genomes for the mutated genes that cause cancer – either oncogenes that are upregulated or tumor suppressor genes that are downregulated. These mutations result in changes in the sequence of proteins, the products of which are dangerous new stuff.

"But this new mechanism of corrupted poly(A) tails opens up a new way in which a gene can be activated or inactivated without a mutation. Nobody has ever looked for the positions of these tails in the past – and it wouldn't' show up by genetic sequencing," Bentley says.

In fact, the poly(A) tails are generally invisible to the traditional techniques of cancer scientists. That's why it may take Bentley's view from outside this cancer science box to discover an answer.

"I'm not actually a cancer scientist," admits Bentley. "In fact, I've never had a grant from the NCI before. It's only through the generosity of researchers at the CU Cancer Center including Ross Camidge in lung

cancer and Anthony Elias in breast cancer that I've been able to frame my lab's rather unique expertise in the maturation of mRNA in terms of its potential clinical impact on cancer."

"The collegiality on this campus made this project possible," Bentley says.

In a year we'll know if this nexus of diverse scientific expertise along with more than a quarter million dollars from the NCI will result in an answer to one of cancer science's most provocative questions: how mRNA tails promote cancer. The answer could provide an entirely new way to intervene in the chain of events that leads from bad genes to cancerous proteins.

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