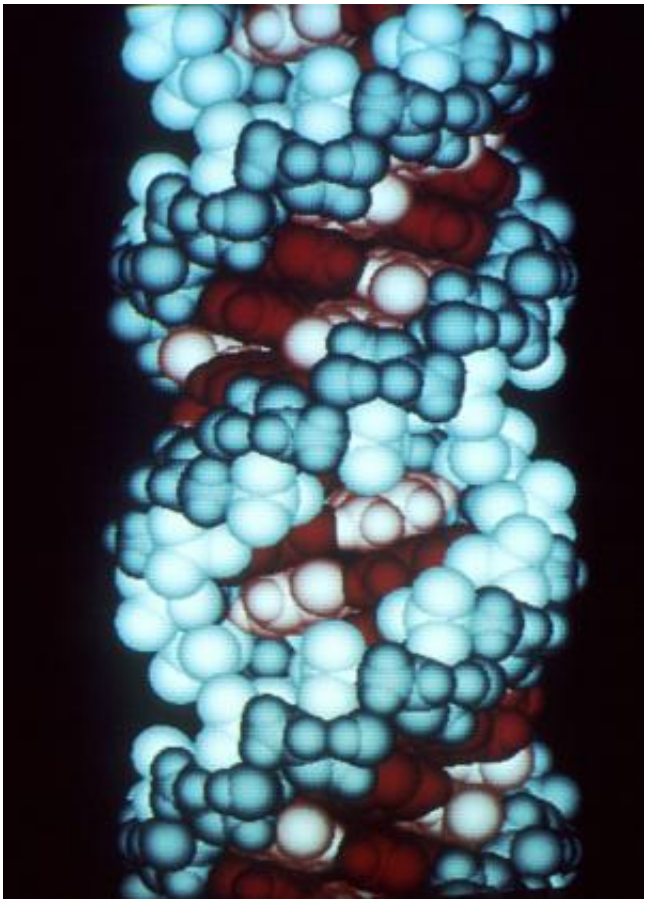
New target for anticancer drugs—RNA

April 6 2015



This is a computer graphic of an RNA molecule. Credit: Richard Feldmann/Wikipedia

Most of today's anticancer drugs target the DNA or proteins in tumor cells, but a new discovery by University of California, Berkeley, scientists unveils a whole new set of potential targets: the RNA

intermediaries between DNA and proteins.

This RNA, called messenger RNA, is a blueprint for making proteins. Messenger RNA is created in the nucleus and shuttled out into the cell cytoplasm to hook up with protein-making machinery, the ribosome. Most scientists have assumed that these mRNA molecules are, aside from their unique sequences, generic, with few distinguishing characteristics that could serve as an Achilles heel for targeted drugs.

Jamie Cate, UC Berkeley professor of molecular and cell biology, and postdoctoral fellows Amy Lee and Philip Kranzusch have found, however, that a small subset of these mRNAs - most of them coding for proteins linked in some way to cancer - carry unique tags. These short RNA tags bind to a protein, eIF3 (eukaryotic initiation factor 3), that regulates translation at the ribosome, making the binding site a promising target.

"We've discovered a new way that human cells control cancer gene expression, at the step where the genes are translated into proteins. This research puts on the radar that you could potentially target mRNA where these tags bind with eIF3," Cate said. "These are brand new targets for trying to come up with small molecules that might disrupt or stabilize these interactions in such a way that we could control how cells grow."

These tagged mRNAs - fewer than 500 out of more than 10,000 mRNAs in a cell - seem to be special in that they carry information about specific proteins whose levels in the cell must be delicately balanced so as not to tip processes like cell growth into overdrive, potentially leading to cancer.

Surprisingly, while some of the tags turn on the translation of mRNA into protein, others turn it off.

"Our new results indicate that a number of key cancer-causing genes - genes that under normal circumstances keep cells under control - are held in check before the proteins are made," Cate said. "This new control step, which no one knew about before, could be a great target for new anticancer drugs.

"On the other hand," he said, "the tags that turn on translation activate genes that cause cancer when too much of the protein is made. These could also be targeted by new anticancer drugs that block the activation step."

The new results will be reported April 6 in an advance online publication of the journal *Nature*. Cate directs the Center for RNA Systems Biology, a National Institutes of Health-funded group developing new tools to study RNA, a group of molecules increasingly recognized as key regulators of the cell.

mRNA a messenger between DNA and ribosome

While our genes reside inside the cell's nucleus, the machinery for making proteins is in the cytoplasm, and mRNA is the messenger between the two. All the DNA of a gene is transcribed into RNA, after which nonfunctional pieces are snipped out to produce mRNA. The mRNA is then shuttled out of the nucleus to the cytoplasm, where a so-called initiation complex gloms onto mRNA and escorts it to the ribosome. The ribosome reads the sequence of nucleic acids in the mRNA and spits out a sequence of amino acids: a protein.

"If something goes out of whack with a cell's ability to know when and where to start protein synthesis, you are at risk of getting cancer, because you can get uncontrolled synthesis of proteins," Cate said. "The proteins are active when they shouldn't be, which over-stimulates cells."

The protein eIF3 is one component of the initiation complex, and is itself made up of 13 protein subunits. It was already known to regulate translation of the mRNA into protein in addition to its role in stabilizing the structure of the complex. Overexpression of eIF3 also is linked to cancers of the breast, prostate and esophagus.

"I think eIF3 is able to drive multiple functions because it consists of a large complex of proteins," Lee said. "This really highlights that it is a major regulator in translation rather than simply a scaffolding factor."

Lee zeroed in on mRNAs that bind to eIF3, and found a way to pluck them out of the 10,000+ mRNAs in a typical human cell, sequenced the entire set and looked for eIF3 binding sites. She discovered 479 mRNAS - about 3 percent of the mRNAs in the cell - that bind to eIF3, and many of them seem to share similar roles in the cell.

"When we look at the biological functions of these mRNAs, we see that there is an emphasis on processes that become dysregulated in cancer," Lee said. These involve the cell cycle, the cytoskeleton, and programmed cell death (apoptosis), along with cell growth and differentiation.

"Therapeutically, one could screen for increased expression of eIF3 in a cancer tissue and then target the pathways that we have identified as being eIF3-regulated," she said.

Lee actually demonstrated that she could tweak the mRNA of two cancer-related genes, both of which control cell growth, to stop cells from becoming invasive.

"We showed that we could put a damper on invasive growth by manipulating these interactions, so clearly this opens the door to another layer of possible anticancer therapeutics that could target these RNA-binding regions," Cate said.

The work was funded by a grant from NIH's National Institute of General Medical Sciences to the Center for RNA Systems Biology.

"A goal of systems biology is to map entire biological networks, such as genes and their regulatory mechanisms, to better understand how those complex networks function and can contribute to disease," said Peter Preusch, chief of the biophysics branch of NIGMS. "This center is using cutting-edge technology to interrogate the structure and function of many RNAs at a time, which is helping piece together RNA's regulatory components."

More information: eIF3 targets cell-proliferation messenger RNAs for translational activation or repression, DOI: 10.1038/nature14267

Provided by University of California - Berkeley