Non-specific and specific RNA binding proteins found to be fundamentally similar

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Researchers from Case Western Reserve University School of Medicine have found unexpected similarities between proteins that were thought to be fundamentally different.

The team studied how proteins bind to RNA, a process required for gene expression. It is known that some proteins only bind RNAs with certain sequences. Other proteins have been deemed "non-specific" because they interact with RNAs at seemingly random places. But the Case Western Reserve team has published a new study in *Nature* showing that non-specific proteins actually do have the ability to be specific about where they bind to RNA – seeking out and binding with particular sequences of nucleotides.

"There seems to be no such thing as specific or non-specific proteins; in essence, they are all specific. But they use their specificity differently," said Eckhard Jankowsky, PhD, co-senior author and professor in the Center for RNA Molecular Biology at the School of Medicine. "Our findings advance understanding of how proteins and nucleic acids control gene expression, which leads to insights into how this control is lost or altered in cancer, viral infections and other diseases."

The Case Western Reserve research team developed a new method for measuring proteins binding to thousands of different RNA molecules, called High Throughput Sequencing Kinetics (HITS-KIN). Applicable to many biologic fields, the approach allows researchers to analyze large numbers of mutations at protein binding sites in DNA or RNA quickly.

HITS-KIN allows scientists to complete experiments in days that previously would have taken years to finish.

"By combining traditional biochemical methods with next-generation sequencing technology, we can now do one experiment with thousands of different RNAs, while before we were limited to analyzing only one RNA molecule at a time," said Michael E. Harris, PhD, co-senior author and associate professor of biochemistry at the School of Medicine.

Defects in the interactions between RNA and binding proteins underlie numerous human diseases including cancer and neurodegenerative diseases. This insight into how molecules interact is a critical step toward the development of novel strategies for treating human disease.

"The Case Western Reserve researchers' new findings may suggest ways to design drugs targeting a whole class of proteins that bind to DNA and RNA at sites lacking specific recognition sequences, which would guide them into place. Previously, we didn't understand how these proteins recognized where to bind to DNA or RNA, which hampered the design of drugs targeting that activity," said Oleg Barski, PhD, of the National Institutes of Health's National Institute of General Medical Sciences, which partially funded the research. "The research also shows that next-generation sequencing technology can deepen our understanding of these proteins and how they control the inner workings of cells."

Jankowsky and Harris utilized HITS-KIN to analyze how weakly or tightly large numbers of different RNAs bind to a particular protein. Although non-specific proteins were predicted to bind to all RNA sequences with similar affinity, the researchers found the same broad range of binding affinities for the non-specific protein that typically appear for a specific protein.

The authors theorize that the two types of proteins may not differ

fundamentally, but rather use different parts of their affinity spectrum in order to express genes correctly. While specific proteins can connect with their preferred sequences among a cell's many RNA molecules, the preferred RNA sequences of non-specific proteins are not created by the cell. As a result, non-specific proteins are left to bind to the available RNAs with similar affinity for many different RNAs.

"Essentially, each protein has binding preferences. However, the non-specific proteins can bind only to those sequences that are made available to them, whereas the specific proteins are able to bind to their 'first choice' sequences," added Jankowsky.

More information: www.nature.com/nature/journal/ … ull/nature12543.html

Provided by Case Western Reserve University

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