Some existing anti-cancer drugs may act in part by targeting RNA, study shows

June 28 2018

Professor Matthew Disney led the new study. Credit: Scripps Research

Bolstering the notion that RNA should be considered an important drug-discovery target, scientists at Scripps Research have found that several existing, FDA-approved anti-cancer drugs may work, in part, by binding tightly to RNA, the regulators of the basic activities of life within cells. The research offers another approach for tackling diseases that have been considered "undruggable," including amyotrophic lateral sclerosis (ALS), muscular dystrophy, cystic fibrosis and certain cancers.

"Known drugs made in the era when RNAs were not considered drug targets are, in fact, binding RNA, and causing some of the drug's effects by modulating targets that were not previously considered," says chemist Matthew D. Disney, Ph.D., professor on the Florida campus of Scripps Research, who led the study. "We found broad drug classes that bind RNA. There is reason to believe that not only could known drugs bind RNA in a disease setting, but there is more evidence that one should consider RNA as a target in drug-discovery efforts."

While the universe of human proteins consists of about 20,000 varieties, the universe of human RNAs is closer to 200,000, potentially offering other effective opportunities to intervene, Disney says.

The paper, "Approved Anti-Cancer Drugs Target Oncogenic Non-Coding RNAs," appears in the journal *Cell Chemical Biology* June 28.

Most drugs on the market today come in the form of pills that contain active small molecule medicines. Through a process called structure-based drug design, chemists optimize such small molecule drugs to bind selectively and tightly to their biologic targets. The target is generally the pocket of a protein important in disease progression.

But there are limitations to small molecules. Because proteins are large and contain many folds and crevasses, sometimes key disease-driving areas are inaccessible to small molecule drugs. This problem has inspired Disney and other researchers to take a closer look at the roots of diseases. Because RNAs are involved in assembling proteins within cells, some have hypothesized that "undruggable" diseases could be modified prior to protein fabrication, at the RNA level.

Disney says he has encountered skepticism about the value of pursuing RNA-binding small molecule therapeutics. The thought was RNAs presented too challenging a target due to their size, movement, changeability and uncertain specificity. RNAs are shape-shifters, and generally thought to lack clearly defined structures to which a small molecule drug could obviously bind. Yet all along, as the new study shows, existing drugs have been doing just that—and binding defined pockets in an RNA—Disney says.

To explore his hypothesis, Disney devised a system for rapidly testing a large library of existing drugs against a wide variety of RNA molecules. He calls his testing system AbsorbArray.

"Basically, we figured out a way in which we could test millions of combinations of small molecule medicines and RNA folds that bind to each other," Disney says.

With AbsorbArray, the researchers identified the three drugs that bound to one type of microRNA and found they were microRNAs involved in every cancer. The drugs, called kinase- and topoisomerase-inhibitors, interfere with expression of a microRNA called miR-21. In further testing, it became clear that interfering with that microRNA prevented cancer cells from invading tissue.

"This data supports the hypothesis that very average-looking small

molecule drugs can target RNA," Disney says.

Conducting the experiment required using a library of known small molecule drugs, and testing them against another library, of pre-messenger RNA, a process Disney called two-dimensional combinatorial screening. He was assisted in that effort by Arnab K. Chatterjee, Ph.D., at the California Institute for Biomedical Research (Calibr), a division of Scripps Research, which supplied the RNA splicing modulator library for the experiments.

"What is particularly interesting to me as a chemist is how existing compounds that have been tested in the clinic and optimized on one protein target may have additional novel activities in targeting RNA as well," Chatterjee says.

Looking forward, the next question is whether the selectivity and drug-like properties of these anti-cancer compounds will extend to diseases other than cancers, Chatterjee says.

In recent years, the Disney lab has found RNA-binding molecules applicable to many diseases, including ALS, myotonic dystrophy type 2, triple-negative breast cancer, inflammation, cystic fibrosis, Alport syndrome and more. The AbsorbArray findings underscore the likely value of continuing to move these disease-relevant RNA-binding compounds toward a clinical setting, Disney said.

"Drugs that patients take every day apparently target RNA, which is only recently being thought of as a target for small molecule medicines," Disney says. "As new RNAs are found to cause disease, routine medicines may be identified to target them. This would change the perception of RNAs as an afterthought in drug discovery and bring them to the forefront."

Other authors of the study, "Approved Anti-Cancer Drugs Target Oncogenic Non-Coding RNAs," include Sai Pradeep Velagapudi, Matthew G. Costales, Balayeshwanth R. Vummidi, Yoshio Nakai, Alicia J. Angelbello, Tuan Tran, Hafeez S. Haniff, Yasumasa Matsumoto, Zi Fu Wang and Jessica L. Childs-Disney of Scripps Research and Arnab K. Chatterjee of the California Institute for Biomedical Research (CALIBR).

This work was supported by the Scheller Graduate Student Fellowship, a Swiss National Science Foundation Early Postdoc Mobility Fellowship, and the National Institutes of Health (grant 5R01GM097455).

"Drugs that patients take every day apparently target RNA, which is only recently being thought of as a target for small molecule medicines," Disney says. "As new RNAs are found to cause disease, routine medicines may be identified to target them. This would change the perception of RNAs as an afterthought in drug discovery and bring them to the forefront."

More information: Sai Pradeep Velagapudi et al, Approved Anti-cancer Drugs Target Oncogenic Non-coding RNAs, *Cell Chemical Biology* (2018). DOI: 10.1016/j.chembiol.2018.05.015

Provided by The Scripps Research Institute