New drug targets from RNA-binding proteins

Piia Bartos, a senior pharmaceutical researcher at the University of Eastern Finland's School of Pharmacy, is interested in RNA, the proteins that bind RNA, and how this system can be influenced to prevent cancer growth. She studies RNA and the function of the argonaute protein that binds to it using massive simulations.

Molecular dynamics simulations provide insights into how biomolecules interact with each other at the atomic level. Because atoms are in constant motion, the forces between them are calculated and used to determine factors such as the new positions, velocities and energies of the protein atoms. This will provide new information for drug design.

Bartos has been studying RNA-binding proteins (RBPs), which may play a role in cancer treatment. RBPs have been found to play a role in cancer cells, particularly in drug responses and the development of drug resistance. More than 1,500 RBPs have been discovered so far. Changes in the function of these proteins can affect the level of cancer gene expression.

RNA interference (RNAi) is a biochemical mechanism whereby RNA causes the cleavage of messenger RNA in the cell, disrupting gene expression. The researchers who discovered RNAi, **Andrew Fire** and **Craig Mello**, were awarded the Nobel Prize for medicine in 2006. RNAi can be used to switch off the expression of proteins that promote cancer growth.

"We're particularly interested in argonaute proteins which play an important role in RNA-mediated gene silencing. The most important of these is Ago2," says Bartos.

When RNA is bound to Ago2 protein, this combination is called the RNA-Ago2 complex. Argonaute 2 protein binds microRNA molecules in cells.

"As argonaute-2 is a protein that's vital for cell function, it's likely to affect all types of cancer. If it is removed from the cells, the cells will not survive. If its activity could be eliminated in cancer cells, those cells would not survive. This would prevent the growth and spread of cancer cells."

Simulating protein structure to find highly selective drugs

The challenge is that two types of RNA molecules can be bound in the RNA-Ago2 complex. The first inhibits protein production, whereas the second increases it. In the latter case, the production of proteins in cancer cells increases.

"I simulated the function of RNA separately, and also with the Ago-2 protein. I have tried to clarify how Ago-2 complexes differ structurally – that is, when they contain RNA that increases protein production, and when they contain RNA that decreases protein production. We've just finished running the simulations and we're now analysing the results."

Simulations of molecular dynamics can be used to make a kind of video of the movements of Ago2-RNA complexes and to compare the differences between activating and silencing complexes.

The RNA sequence data used in the simulation was obtained from the A.I. Virtanen Institute for Molecular Sciences. Six RNA molecules were used in the simulations, three of which increased protein production and three of which decreased it. For all of these, molecular dynamics simulations were run for about 50 microseconds, or a millionth of a second per system. The simulations placed high demands on the computing resources of the Finnish ELIXIR Node, CSC – IT Center for Science.

"It's a fairly big protein. Along with the RNA and the surrounding water, there are

about 300,000 atoms, and we had to calculate the speed and position of all of them every four femtoseconds."

A femtosecond is a millionth of a billionth of a second. Bartos is aiming to find out whether the shape of the complex changes, and whether a part of the protein moves differently when it has an increasing or decreasing RNA bound to it.

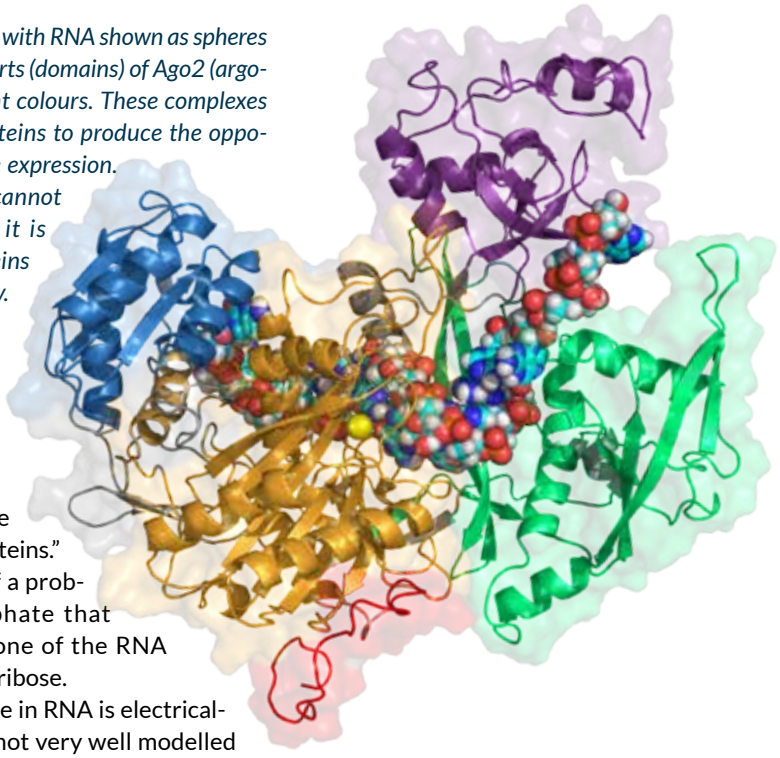
"It's likely that the change in the shape of the complex can indicate that the complex binds to different proteins."

There must therefore be a difference in the structure or movement of the complexes that causes different effects that either increase or decrease gene expression.

By understanding the structural differences between RNA-protein complexes that reduce and increase gene expression, it is possible to design and screen drugs that bind only to the desired complex. According to Bartos, such drugs would be a medical breakthrough, and would offer a new way to treat cancers where protein production is impaired.

"RNA interference-based drugs are a good alternative. These drugs could be more specific and better targeted to the cancer cell than a standard small-molecule cancer drug. With RNA interference, we could, if necessary, block the expression of any protein in a cancer that we wanted to block. So this would give highly selective drugs."

According to Bartos, however, modelling the function of RNA is still a challenge. In simulations, force-field models work well for proteins, but not for RNA.



RNA-Ago2 complex with RNA shown as spheres and the different parts (domains) of Ago2 (argonaute 2) in different colours. These complexes can bind other proteins to produce the opposite effects on gene expression. An effective drug cannot be created unless it is known which proteins it affects in the body.

"The reason for this is that RNA is chemically and physically quite different from proteins."

An example of a problem is the phosphate that forms the backbone of the RNA strand with deoxyribose.

"The phosphate in RNA is electrically charged and is not very well modelled by these current force-field equations. So there's clearly a lot of work to be done in developing the tools."

Drug design has been making great strides on many levels. DeepMind's artificial intelligence AlphaFold can already solve how a sequence becomes a protein structure. It uses known protein structures, and predicts the structure for all known proteins.

Sequencing can be used to identify mutations in cancer, and models can be used to study how mutations affect the action of anticancer drugs.

"For example, the mutation may prevent the cancer drug from binding to the target protein at the drug target, in which case the patient will rarely benefit from the drug."

As computing capacity increases, it will also become possible to simulate larger entities.

"It would be great to simulate a single protein as a part of a larger unit, for instance at the cellular level. We could simulate how the protein interacts with other proteins, cell membranes and cell organelles."

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MORE INFORMATION:

Hanna Baltrukevich & Piia Bartos: RNA-protein complexes and force field polarizability. Front. Chem., 22 June 2023. Sec. Theoretical and Computational Chemistry. Volume 11 - 2023 | https://doi.org/10.3389/fchem.2023.1217506

Milla Kurki et all: **Structure of POPC Lipid Bilayers in OPLS3e Force Field**. Journal of Chemical Information and Modeling. Vol 62/Issue 24 https://pubs.acs.org/doi/full/10.1021/acs.jcim.2c00395

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