High definition nanomovies reveal how RNA dances with drug partners

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(PhysOrg.com) -- Building on a technique they used to produce nanomovies of RNA molecules in motion, researchers have created "high definition" versions of the animations that reveal even more details about how RNA changes shape and binds with drug molecules.

The research, led by Hashim M. Al-Hashimi at the University of Michigan and Ioan Andricioaei at the University of California, Irvine, fuses two methods of gleaning atomic-level information about RNA. It lays the groundwork for a whole new approach to drug design, said Al-Hashimi, associate professor of chemistry and of biophysics.

Al-Hashimi is an expert in the development of NMR experimental methods to visualize the dynamics of biomolecules such as DNA and RNA. The work is described in a paper published online this week in the journal *Nucleic Acids Research*.

Once believed to merely store and relay genetic information, RNA now is known to perform a variety of other functions, from regulating gene expression and other vital cellular processes to serving as a sensor that detects cellular signals and carries out appropriate reactions in response. The versatile molecule also is essential to viruses such as HIV, which have no DNA and instead rely on RNA to both transport and execute genetic instructions for everything the virus needs to invade and highjack its host.

Typically, RNA works by radically changing shape when bound to

something else. The shape changes, in turn, trigger other processes or cascades of events. Al-Hashimi's earlier nanomovies showed how parts of the RNA molecule—which has ladder-like arms connected by a flexible hub or linker—twist, bend and rotate relative to one another. The movies also showed that rather than changing shape in response to encounters with drug molecules, RNA goes through a predictable course of shape changes on its own. Drug molecules simply "wait for the right shape" and attach to RNA when the RNA assumes the particular drug's preferred conformation, Al-Hashimi said.

Unlike animations produced from theoretical calculations—an approach known as molecular dynamics simulations—Al-Hashimi's earlier nanomovies were based on actual NMR data and covered a much longer timescale than the simulations. However, there are limits to how much detail such data-based nanomovies can reveal, Al-Hashimi said.

"Our earlier movies were a great step forward, but they're what I would call low-definition movies. They show the motion of only the helices, not the linker, which is the part to which drugs bind." While the researchers would like to show the motion of every single atom making up the RNA molecule, it's not currently possible—and may never be possible—to collect enough NMR data for that kind of resolution.

"We would need a trillion times more data than we currently can get, just a mind-boggling amount of data," Al-Hashimi said. "There's just no way."

Movies produced with molecular dynamics simulations, on the other hand, provide better resolution. But because they're based on theoretical calculations, it's hard to know how closely they reflect reality, said Irvine's Andricioaei, who is an expert in the development of computational approaches for understanding how biomolecules work.

By marrying the two techniques, Andricioaei, Al-Hashimi and coworkers were able to validate the simulations and combine them with NMR data to produce a "fully resolved, high-definition movie of what RNA does," Al-Hashimi said. "With this hybrid movie, generated from both data and simulations, we can now see the linker and other details that we couldn't see before."

Now the researchers can use the movies as a tool to ask, for example, how changes in the linker affect RNA's ability to carry out its duties and how drugs "decide" which RNA conformation to latch onto. If the researchers can break the drug decision-making code, they may be able to use the approach in the discovery of new drugs.

Provided by University of Michigan (news : web)