# Ancient enzymes function like nanopistons to unwind RNA

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Molecular biologists at The University of Texas at Austin have solved one of the mysteries of how double-stranded RNA is remodeled inside cells in both their normal and disease states. The discovery may have implications for treating cancer and viruses in humans.

The research, which was published this week in *Nature*, found that DEAD-box proteins, which are ancient enzymes found in all forms of life, function as recycling "nanopistons." They use chemical energy to clamp down and pry open RNA strands, thereby enabling the formation of new structures.

"If you want to couple fuel energy to mechanical work to drive strand separation, this is a very versatile mechanism," said co-author Alan Lambowitz, the Nancy Lee and Perry R. Bass Regents Chair in Molecular Biology in the College of Natural Sciences and Director of the Institute for Cellular and Molecular Biology.

In all cellular organisms RNA (ribonucleic acid) plays a fundamental role in the translation of genetic information into the synthesis of proteins. DEAD-box proteins are the largest family of what are known as " RNA helicases," which unwind RNA.

"It has been known for some time that these enzymes do not function like traditional helicases," said Eckhard Jankowsky, professor of biochemistry at Case Western Reserve University Medical School. "The manuscript now provides the critical information that explains how the

unwinding reaction works. It marks a major step towards understanding the molecular mechanics for many steps in RNA biology."

Lambowitz said that the basic insight came when Anna Mallam, a post-doctoral researcher in his lab, hypothesized that DEAD-box proteins function modularly. One area on the protein binds to an ATP molecule, which is the energy source. Another area binds to the double-stranded RNA.

"Once the second domain is latched on to the RNA," said Mallam, "and the first has got its ATP, the 'piston' comes down. It has a sharp edge that drives between the two strands and also grabs on one strand and bends it out of the way."

Lambowitz, Mallam and their colleagues uncovered this mechanism in Mss116p, a DEAD-box protein in yeast. The mechanism is almost certainly universal to the entire family of the proteins, however, and therefore to all domains of life.

"Every DEAD-box protein that we know about has the same structure," said Lambowitz, "and they all presumably use the same mechanism."

Lambowitz said that the Mss116p proteins are particularly useful as a universal remodeling device because they can bind to any RNA.

"It recognizes the geometry of double-stranded RNA," he said. "It doesn't care about the sequence, and doesn't care about what it that particular RNA molecule's function is. It just sees it and binds and for that reason can be incorporated into many different cellular processes."

This flexibility of DEAD-box proteins is essential to the functioning of healthy cells, which rely on a range of RNA molecules for basic processes, including protein synthesis.

It's also hijacked in cancers, where over-expression of DEAD-box proteins may help drive uncontrolled cell proliferation, and in infections caused by bacteria, fungi, and viruses, which rely on specific DEAD-box proteins for their propagation.

"This is basic science," said Lambowitz. "Its major significance is in understanding, at the root, how this mechanism works. But when you understand how DEAD-box proteins function both in normal cellular processes and in disease processes, you can absolutely begin to think about how they might be targeted in things like cancer and viruses."

"You can even envision, in the far future, how they be incorporated into artificial nanomachines, for switches and other mechanical devices inside and outside the cell."

Provided by University of Texas at Austin

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