Molecular machine may lead to new drugs to combat human diseases

February 18 2005

The crystallized form of a molecular machine that can cut and paste genetic material is revealing possible new paths for treating diseases such as some forms of cancer and opportunistic infections that plague HIV patients.
Purdue University researchers froze one of these molecular machines, which are chemical complexes known as a Group I intron, at mid-point in its work cycle. When frozen, crystallized introns reveal their structure and the sites at which they bind with various molecules to cause biochemical reactions. Scientists can use this knowledge to manipulate the intron to splice out malfunctioning genes, said Barbara Golden, associate professor of biochemistry. Normal genes then can take over without actually changing the genetic code.

The results of the Purdue study are published in the January issue of the journal Nature Structural and Molecular Biology.

"In terms of human health, Group I introns are interesting because they cause their own removal and also splice the ends of the surrounding RNA together, forming a functional gene," Golden said. "We can design introns and re-engineer them so they will do this to RNA in which we're interested."

Once thought of as genetic junk, introns are bits of DNA that can activate their own removal from RNA, which translates DNA's directions for gene behavior. Introns then splice the RNA back together. Scientists are just learning whether many DNA sequences previously

believed to have no function actually may play specialized roles in cell behavior.

While humans have introns, they don't have Group I introns. Many pathogens that cause human diseases, however, do have Group I introns, including the HIV opportunistic infections pneumocystis, a form of pneumonia, and thrush, an infection of tissues in the oral cavity. This makes introns a potential target for therapeutics against these diseases by using a strategy called targeted trans-splicing in which introns are manipulated to cut out malfunctioning genes.

Introns' unique capability of cutting and pasting apparently has been conserved since life evolved.

"It's thought that RNA, or a molecule related to RNA, possibly were the first biomolecules, because they are capable of both performing work and carrying around their own genetic code," Golden said.

She and her research team used an intron from a bacteriophage, a molecule that attacks bacteria, to obtain an intron crystal structure trapped in the middle of the cutting and pasting cycle. As introns proceed through their work cycle, they change shape by folding and bending. By crystallizing the complex at various stages, the scientists can determine and study its three-dimensional structure and learn how it is able to carry out its biochemical work.

The Group I intron at its work cycle's mid-point, which Golden crystallized, is unreactive but reveals many of the interactions between the RNA and the molecules that it activates, she said.

"Knowing the structure can help us engineer molecules to behave better," Golden said. "It's very hard to find targets in cells because cells are organized in ways we still don't fully understand. This crystal structure

shows us where the best targets are for modifying genetic defects."

The crystal structure of this Group I intron also will allow scientists to form models of hundreds of other introns in the same family and provide possibilities for new treatments for a wide variety of diseases, she said.

Other scientists now will use the information gleaned from this study in an attempt to develop new drugs, Golden said.

Introns were unknown until the late 1970s, and scientists are still investigating their function. Crystallization of the complex is one tool to determine their purpose.

Two intron structures in different stages of the cycle have been crystallized previously, and the targeted trans-splicing technique has been used to repair hemoglobin infected with sickle cell anemia. The new structure provides scientists with tools to expand on ways to harness this molecular machine, Golden said.

The other researchers on this study were Hajeong Kim, graduate student, and Elaine Chase, research associate, both of the Purdue Department of Biochemistry. Golden also is a scientist in the Purdue Cancer Center, a National Cancer Institute designated research facility.

Source: Purdue University