MedicalXpress

Study reveals intermediary steps of genetic encoding for the first time

March 27 2009

In a new study this week in *Nature*, researchers at Brandeis University and the MRC Laboratory of Molecular Biology (Cambridge, U.K.) for the first time shed light on a crucial step in the complex process by which human genetic information is transmitted to action in the human cell and frequently at which point genetic disease develops in humans.

The scientists report that they were able to crystallize a very large complex of a macromolecular "machine" in the human cell and determine its structure or what it actually looks like, thereby zeroing in on the process of genetic encoding. Importantly, 15 to 20 percent of all human genetic disorders, including muscular dystrophy, are caused by defects in this genetic encoding process known as RNA splicing.

Using x-ray crystallography, the scientists for the first time were able to create a three-dimensional structure of an integral complex of the human spliceosome, which consists of specialized RNA and protein subunits. The spliceosome's job is to modify the message relayed from our genetic material—DNA—by clipping, or splicing, genetic bits in such a manner that they are acceptable for translation into protein. Importantly, the spliceosome also rearranges the genetic bits of the message in such a way that it can generate multiple and varied proteins which can and do have dramatic effects on human development, said lead author and Brandeis biochemist Daniel Pomeranz Krummel.

"The process of RNA splicing is vital to human cell development and survival," said Pomeranz Krummel. "In this process, the regions of our

DNA encoding for protein are removed from non-encoding regions and brought together—quite often in alternative arrangements. Defects in this process can have disasterous repercussions in the form of genetic disorders," said Pomeranz Krummel, adding that neuronal development can be particularly affected when things go awry. Indeed, defects in this process have recently been implicated in various human neurological disorders, including epilepsy.

Specifically, this macromolecular machine clips, or splices, gene sequences transcribed as part of a precursor to the mRNA, removing them before the final mRNA product is translated into protein. The spliceosome must clip these sequences, known as introns, at the right place in the precursor mRNA.

"In human cells one gene can be made into a variety of proteins, so if the process just goes slightly wrong, the genetic alteration can lead to incredible disaster; yet on the other hand, this incredible complexity has led to our amazing evolutionary progress," said Pomeranz Krummel. "The human genome is not terribly different from the earthworm's with regards to its size, but the process of RNA splicing that occurs in our cells is different. The fundamental difference between us and the earthworm is that our cells have evolved to utilize this process of RNA splicing to generate a whole other dimension to the transmission of genetic information."

Pomeranz Krummel's lab will next focus on understanding how this complex interacts with other macromolecular machines in the human cell. The study was funded by the Medical Research Council (U.K.) and the Human Frontier Science Program.

Source: Brandeis University