Scientists discover new way in which ubiquitin modifies transcriptional machinery

December 18 2008

During gene transcription – the process inside the nucleus of cells by which DNA, the genetic material, is copied into RNA molecules – a large, ever-changing multiprotein complex is enlisted to assist the DNA-copying enzyme in its challenging job.

Like an exquisitely choreographed dance, each step in the process has to be performed with precision, in order for the copy to be accurate and useful in subsequent events. These events culminate in a version of the RNA copy exiting the nucleus and serving as the template for the production of new proteins.

Scientists have documented a host of mechanisms involved in the assembly and behavior of the "helper" protein complex. A team at Cold Spring Harbor Laboratory (CSHL) has now discovered a mechanism, which, according to Professor William P. Tansey, Ph.D., "provides a paradigm for how the components [of the helper complex] could be disassembled and how the complex falls apart." Their results will appear in the December 16th issue of *Proceedings of the National Academy of Sciences*.

A "wedge" in transcription

One of the mechanisms that influences critical interactions in transcription is called ubiquitylation. It involves the addition of small protein molecules called ubiquitin to other, larger proteins. When

ubiquitin "tags" are added to these larger molecules, it has the effect of marking them for destruction. Tansey's team has previously characterized how the ubiquitin-triggered destruction of transcription factors – proteins that help switch on genes – was connected to the regulation of gene activity.

The addition of ubiquitin, however, was later found, in other contexts, to modify proteins in non-destructive ways, too. This suggested to Tansey the existence of a more benign link between transcription and ubiquitylation. Working with yeast cells, Tansey's team has now identified this link: a protein called Asr1.

Understanding its role has enabled Tansey and colleagues to more comprehensively grasp how ubiquitin functions. They have discovered that Asr1 "glues" ubiquitin on to specific spots in the DNA-copying enzyme, called RNA polymerase II (abbreviated by scientists as RNA pol II). This enzyme is composed of 12 modules, each with a distinct function. When Asr1 binds to the enzyme, bits of ubiquitin that glom onto it form little wedge-like features between the enzyme's different modules. This causes two of the 12 modules to be jettisoned from the enzyme, thereby "inactivating" it. "The activity of Asr1 is an example of how ubiquitin can regulate gene transcription by using its non-destructive functions to pull a complex apart," says Tansey.

A new class of proteins

Along with other proteins that resemble it in structure, Asr1 is present in most multicellular organisms, and appears to be well conserved in most species, from yeast to humans. The fact that evolution has "preserved" them is an indication that this class of proteins performs an important job.

The CSHL team made another notable discovery. They found that Asr1

has the unique ability of homing in on RNA pol II molecules that are actively turning on genes, while at the same time ignoring otherwise similar enzymes that remain idle. This fact, according to Tansey, suggests that Asr1 is a "negative" regulator of gene transcription.

He hypothesizes that Asr1 might selectively glom on to RNA pol II molecules that are making mistakes in copying or copying DNA in the wrong location. It is also possible, according to Tansey, that Asr1's ubiquitin-adding ability enables it to help terminate the normal transcription process. In addition to pursuing experimental evidence of these possibilities, Tansey's team is now also hunting for other Asr1-like ubiquitin-adding proteins that may influence gene activity.

Source: Cold Spring Harbor Laboratory