Scientists identify critical 'quality control' for cell growth

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Scientists from the Florida campus of The Scripps Research Institute have identified a series of intricate biochemical steps that lead to the successful production of proteins, the basic working units of any cell.

The study, which appears in the July 6, 2012 edition of the journal *Cell*, sheds light on the assembly of a structure called the ribosome, a large and complex protein-producing machine inside all living cells. Ribosomes are the targets of many commercially used antibiotics and represent a promising area of research because of the importance of ribosome assembly and function for cell growth. There are well-established links between defects in ribosome assembly and cancer, making this pathway a potential new target for anti-cancer drugs.

"With important cellular machines like ribosomes, it makes sense that some process exists to make sure things work correctly," said Katrin Karbstein, a Scripps Research associate professor who led the study. "We've shown that such a quality control function exists for ribosomal subunits that use the system to do a test run but don't produce a protein. If the subunits don't pass, there are mechanisms to discard them."

Protein Production Line

As part of the protein-production process called "translation," the ribosome decodes information carried in messenger RNA (mRNA) to produce a protein—a chain of amino acids.

To produce mature, functioning ribosomal RNAs (rRNAs), the body first makes precursor rRNAs that can be processed into mature ones. In human cells, this is done in two stages—the first occurs in the nucleolus, a protein-nucleic acid structure inside the nucleus, and finally in the cytoplasm, the basic cellular stew where protein translation occurs.

In the cytoplasm, these pre-mature ribosomal subunits encounter large pools of mature subunits, messenger RNA, and numerous assembly factors and translation factors that help complete the process.

During the final maturation process, various assembly factors prevent the translation process from acting on the subunits prematurely, which would result in their rapid degradation or in the production of incorrectly assembled proteins, both processes with potentially lethal outcomes for the cell.

Trial Run

While the work of these assembly factors explains how premature translation is blocked, their presence raises another important question, Karbstein said—Does the conversion of inactive assembly intermediates into mature ribosomes require checkpoints to assure that subunits are functional?

In the study, Karbstein and her colleagues were able to show that during this translation-like cycle the newly made ribosome subunit initially joins with its complementary preexisting subunit to form a much larger complex through the influence of a single translation factor.

This large ribosome complex contains no messenger RNA, which is blocked by assembly factors, and thus produces no protein. Once the major functions of the smaller ribosome subunit have been inspected and approved, another translation factor breaks up the complex and

actual protein production occurs.

"What is important here is that the test cycle involves the same translational factors that are involved in normal translation," Karbstein said. "It's the most elegant and efficient way to produce perfect ribosomes."

Interestingly, the study noted, the majority of assembly factors involved in this translation-like test cycle are conserved in creatures ranging from one-celled organisms to humans, suggesting that this evolutionary mechanism is common to all.

More information: "Joining of 60S Subunits and a Translation-like Cycle in 40S Ribosome Maturation" *Cell*, 2012.

Provided by Scripps Research Institute