Researchers discover a protein that regulates the hierarchical organisation of ribosome development

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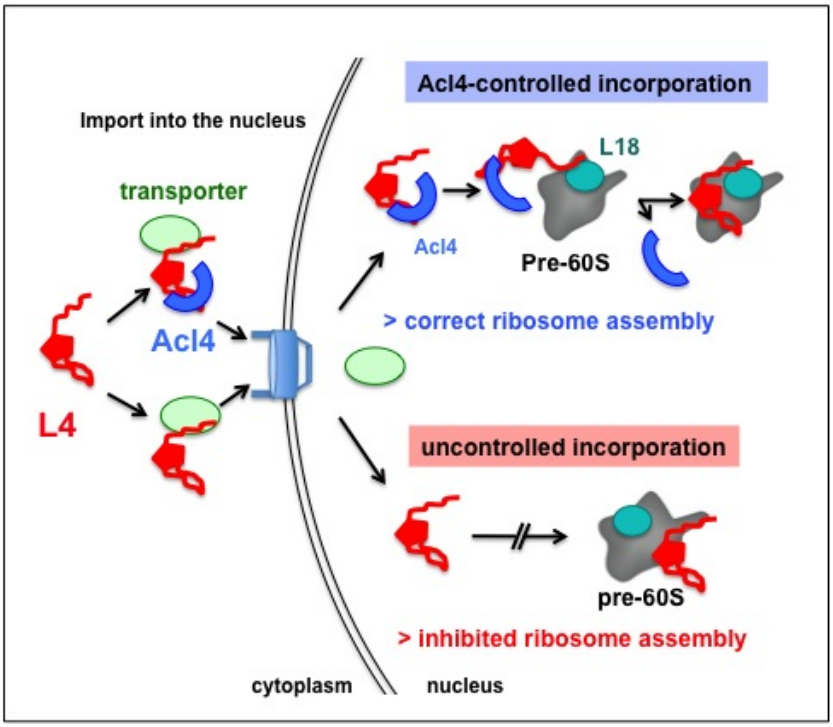


Figur 1 – Model of assembly of the ribosomal protein L4 into the pre-ribosome, catalyzed by Acl4 (upper scheme) and uncontrolled in the absnece of Acl4 (lower scheme)

Model of assembly of the ribosomal protein L4 into the pre-ribosome

Ribosomes are vital to the function of all living cells. Using the genetic information from RNA, these large molecular complexes build proteins by linking amino acids together in a specific order. Scientists have known for more than half a century that these cellular machines are themselves made up of about 80 different proteins, called ribosomal proteins, along with several RNA molecules and that these components are added in a particular sequence to construct new ribosomes, but no one has known the mechanism that controls that process.

Now researchers from Caltech and Heidelberg University have combined their expertise to track a ribosomal protein in yeast all the way from its synthesis in the cytoplasm, the cellular compartment surrounding the nucleus of a cell, to its incorporation into a developing ribosome within the nucleus. In so doing, they have identified a new chaperone protein, known as Acl4, that ushers a specific ribosomal protein through the construction process and a new regulatory mechanism that likely occurs in all eukaryotic cells.

The results, described in a paper that appears online in the journal *Molecular Cell*, also suggest an approach for making new antifungal agents.

The work was completed in the labs of André Hoelz, assistant professor of chemistry at Caltech, and Ed Hurt, director of the Heidelberg University Biochemistry Center (BZH).

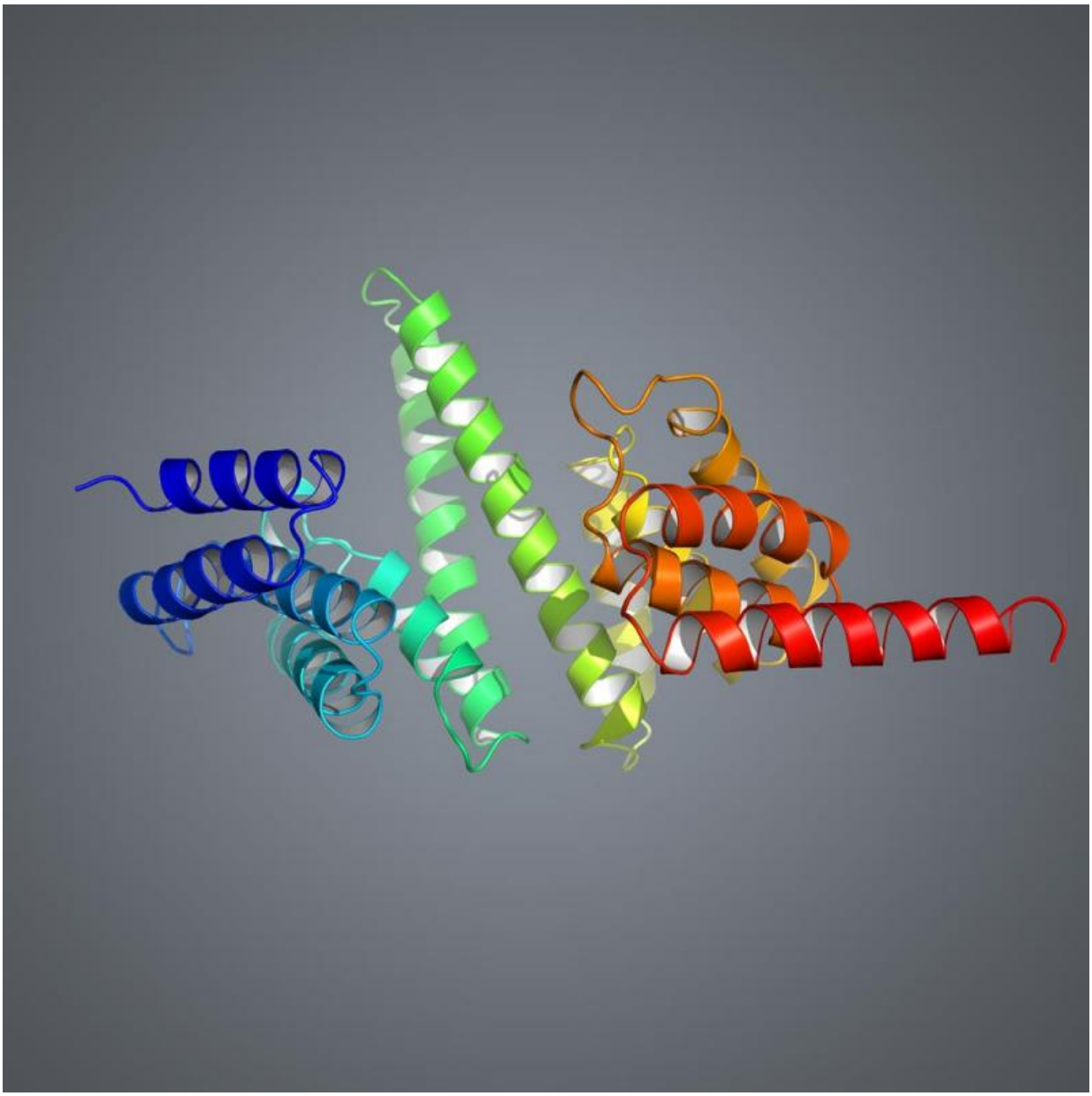
"We now understand how this chaperone, Acl4, works with its ribosomal protein with great precision," says Hoelz. "Seeing that is kind of like being able to freeze a bullet whizzing through the air and turn it around and analyze it in all dimensions to see exactly what it looks like."

That is because the entire ribosome assembly process—including the synthesis of new ribosomal proteins by ribosomes in the cytoplasm, the

transfer of those proteins into the nucleus, their incorporation into a developing ribosome, and the completed ribosome's export back out of the nucleus into the cytoplasm—happens in the tens of minutes timescale. So quickly that more than a million ribosomes are produced per day in mammalian cells to allow for turnover and cell division. Therefore, being able to follow a ribosomal protein through that process is not a simple task.

Hurt and his team in Germany have developed a new technique to capture the state of a ribosomal protein shortly after it is synthesized. When they "stopped" this particular flying bullet, an important ribosomal protein known as L4, they found that its was bound to Acl4.

Hoelz's group at Caltech then used X-ray crystallography to obtain an atomic snapshot of Acl4 and further biochemical interaction studies to establish how Acl4 recognizes and protects L4. They found that Acl4 attaches to L4 (having a high affinity for only that ribosomal protein) as it emerges from the ribosome that produced it, akin to a hand gripping a baseball. Thereby the chaperone ensures that the ribosomal protein is protected from machinery in the cell that would otherwise destroy it and ushers the L4 molecule through the sole gateway between the nucleus and cytoplasm, called the nuclear pore complex, to the site in the nucleus where new ribosomes are constructed.



Crystal structure of the assembly chaperone of ribosomal protein L4 (Acl4) that picks up a newly synthesized ribosomal protein when it emerges from the ribosome in the cytoplasm, protects it from the degradation machinery, and delivers it to the assembly site of new ribosomes in the nucleus. Credit: Ferdinand Huber/Caltech

"The ribosomal protein together with its chaperone basically travel through the nucleus and screen their surroundings until they find an assembling ribosome that is at exactly the right stage for the ribosomal protein to be incorporated," explains Ferdinand Huber, a graduate student in Hoelz's group and one of the first authors on the paper. "Once found, the chaperone lets the ribosomal protein go and gets recycled to go pick up another protein."

The researchers say that Acl4 is just one example from a whole family of chaperone proteins that likely work in this same fashion.

Hoelz adds that if this process does not work properly, ribosomes and proteins cannot be made. Some diseases (including aggressive leukemia subtypes) are associated with malfunctions in this process.

"It is likely that human cells also contain a dedicated assembly chaperone for L4. However, we are certain that it has a distinct atomic structure, which might allow us to develop new antifungal agents," Hoelz says. "By preventing the chaperone from interacting with its partner, you could keep the cell from making new ribosomes. You could potentially weaken the organism to the point where the immune system could then clear the infection. This is a completely new approach."

More information: "Coordinated ribosomal L4 protein assembly into the pre-ribosome is regulated by its eukaryote-specific extension." *Molecular Cell* (April 30, 2015), DOI: 10.1016/j.molcel.2015.03.029

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