How ribosomes are like Russian dolls

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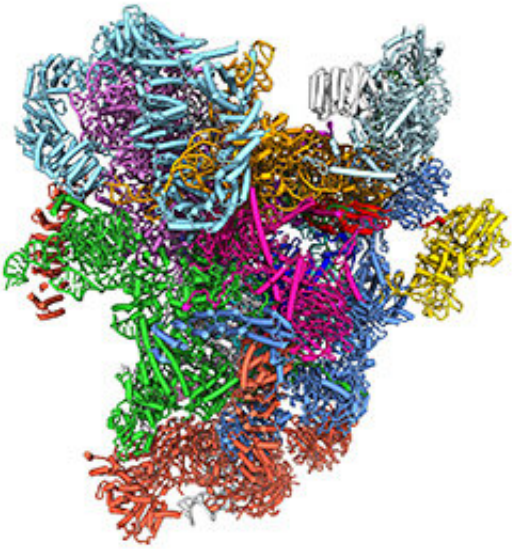

Precurser of the 40S subunit. Credit: Beckmann group

Maturation of the ribosome is a complex operation. Work by an LMU team now shows that the 90S precursor of the small 40S subunit undergoes a "molting" process, during which it progressively discards its outermost components.

Protein synthesis, programmed by the genetic information encoded in the DNA, is perhaps the most crucial process that takes place in biological cells. Proteins are indispensable for all organisms, because they are responsible for performing a vast range of biological functions.

Indeed, the molecular machines that put proteins together—which are known as ribosomes—are themselves partly made up of specific proteins. The second vital ingredient of every ribosome is a small set of specific RNAs, which serve as scaffolds to which ribosomal proteins can be specifically attached. The synthesis of ribosomes is therefore an extremely complex, multistep process, which includes both assembly and maturation stages. This complexity explains why many of the details of the whole operation are still incompletely understood. Now a group of researchers led by Professor Roland Beckmann at LMU's Gene Center has obtained new insights into the maturation phase that gives rise to the small subunit of the functional ribosome in brewer's yeast. The study, which was carried out in collaboration with colleagues based in Heidelberg, appears in the journal *Science*.

In the cells of higher organisms, mature ribosomes are composed of two distinct subunits, each of which contains a long ribosomal RNA (rRNA) molecule (called 18S in the small and 25S in the large subunit in yeast). The subunits interact with one another and with the messenger RNAs that program the synthesis of each protein. In yeast, the smaller 40S subunit is derived from a much larger precursor complex called the 90S pre-ribosome. The 90S precursor particle contains a single (35S) RNA molecule. The RNAs ultimately associated with each mature subunit are produced by the removal of specific internal and end-fragments. However, one of the segments the RNA found in the 90S precursor plays an important role in ensuring that the mature 18S rRNA in the 40S subunit folds into its correct three-dimensional form.

How the processing of the 35S rRNA is achieved has so far been unclear. The general idea was that, as the 40S subunit matures, the processing steps that give rise to the 18S rRNA take place, and the mature 40S particle eventually 'emerges' from the 90S precursor. The new study adds new details, which reveal that the process is rather more complicated than that. For a start, a specific enzyme (Dhr1) is required

to ensure that the initial cleavage of the 35S rRNA precursor occurs at the right position. Dhr1 first exposes the cleavage site, enabling it to interact with the enzyme Utp24, which cuts the correct fragment off one end of the 35S rRNA.

Shedding takes place stepwise

In addition, the "emergence" of the 40S subunit entails an ordered series of reactions in which the outer shell of the 90S particle is progressively dissociated from the 40S. "It doesn't just go plop," Beckmann remarks. The process is actually reminiscent of the molting of an insect—shedding of the integument takes place layer by layer. "It's rather like those Russian dolls. When you open one, you find a smaller one nestled inside," says Beckmann. And with the aid of cryo-electron microscopy, the specialists in Munich were able to discriminate between the different three-dimensional complexes characteristic of each step in the process. Earlier biochemical experiments performed by a team at the Center for Biochemistry at Heidelberg University (BZH), led by Professor Ed Hurt, had already cast doubt on the previous en bloc model by providing evidence for the idea that shedding of the outer layers of the 90S particle took place stepwise.

The elucidation of such mechanisms is not only of interest from the point of view of basic research. As Beckmann points out, more and more disorders have been shown to be related to a lack of intact ribosomes. When errors occur in the assembly and maturation of these delicate and intricate molecular machines, they may ultimately lead to a relative dearth of ribosomes, which then perturbs the delicate equilibrium between protein synthesis and degradation. Among the resulting syndromes are diverse forms of muscle atrophy, growth anomalies, anemias and certain cancers.

More information: Jingdong Cheng et al. 90S pre-ribosome

transformation into the primordial 40S subunit, *Science* (2020). DOI: 10.1126/science.abb4119