MOLECULAR BIOLOGY

The Eukaryotic Ribosome

New crystal structures break impasse, offer insight into how eukaryotes synthesize proteins.

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The past decade has seen a remarkable advance in our understanding of ribosomes, the large protein-RNA machines in all cells that use genetic information to synthesize proteins in a process known as translation. Ribosomes from all species consist of two subunits: a small subunit that decodes messenger RNA (mRNA), and a large subunit that catalyzes peptide bond formation between the growing polypeptide chain and each new amino acid. In 2000, researchers determined the atomic structures of the small and large ribosome subunits from bacteria and archaea, respectively. This has resulted in a dramatic increase in our understanding of translation in prokaryotes (*1*). On page 730 of this issue, Rabl *et al*. take an important step toward doing the same for eukaryotic translation. They offer a crystal structure of the small ribosomal subunit, together with a translation initiation protein, from the eukaryotic protozoan *Tetrahymena thermophila* (*2*). This structure, together with a crystal structure of the eukaryotic ribosome from the yeast *Saccharomyces cerevisiae* at a resolution of 4.15 Å (*3*) and a cryoelectron microscopy (cryo-EM) structure of a translating plant ribosome from *Triticum aestivum* at 5.5 Å (*4*, *5*), represents a breakthrough in studying translation in eukaryotes.

Many core functions such as peptidyl transfer, decoding, translocation, and (possibly) the activation of guanosine triphosphatases are conserved between bacteria and eukaryotes. However, eukaryotic ribosomes are about 50% larger, with the smaller 40*S* and larger 60*S* subunits making up the 80*S* ribosome. Only about one-third of the 80 to 90 ribosomal proteins have bacterial counterparts, and another one-third have archaeal homologs. The remaining one-third are unique to eukaryotes. Eukaryotic translation is also more complex and highly regulated (*6*), especially during initiation, which requires about a dozen initiation factors, many of which are large multisubunit complexes themselves (*7*). In addition, viruses can bypass the normal initiation process by using special sequences in their mRNAs that bind directly to the ribosome and allow initiation without the full set of factors. The ribosome is also involved in processes such as mRNA decay, as well as regulation and surveillance through mechanisms not present in bacteria (*8*). However, progress in understanding eukaryotic translation has been hindered by the lack of high-resolution structures of the eukaryotic ribosome.

Over the past decade, several groups have tried to crystallize the eukaryotic ribosome with little success, suggesting that there might be insurmountable problems. The two recent crystal structures have broken this impasse. For the yeast 80*S* ribosome (*3*), the investigators used glucose starvation, which inhibits initiation (*9*), to produce homogeneous empty ribosomes. Rabl *et al*. conducted an exhaustive search of a dozen species before finally obtaining well-diffracting crystals of a protozoan 40*S* complex (*2*). So it is not clear that these structures provide general lessons for the crystallization of new large complexes.

All of these structures are major advances in the field, but differences among them demonstrate the importance of resolution. At the lower resolution of the plant cryo-EM structures (*4*, *5*), much of the RNA and proteins could be modeled, but the topology of a eukaryotic-specific insertion in the rRNA and the secondary structures of several proteins do not agree with those of the crystal structures. This suggests that using cryo-EM to study the eukaryotic ribosome will be most powerful when its unique ability to visualize biologically interesting states is combined with an accurate reference structure that can be used for modeling, as has been the case with the bacterial ribosome (*10*). The intermediate resolution of the yeast 80*S* crystal structure (*3*) meant that investigators could not completely interpret it, and the traces of several proteins disagree in detail with those of the 40*S* structure. Because these authors already have data at a resolution of 3 Å, this structure must be regarded as an initial progress report that will quickly be superseded.

Although the resolution of Rabl *et al*.'s structure of the protozoan 40*S* subunit with

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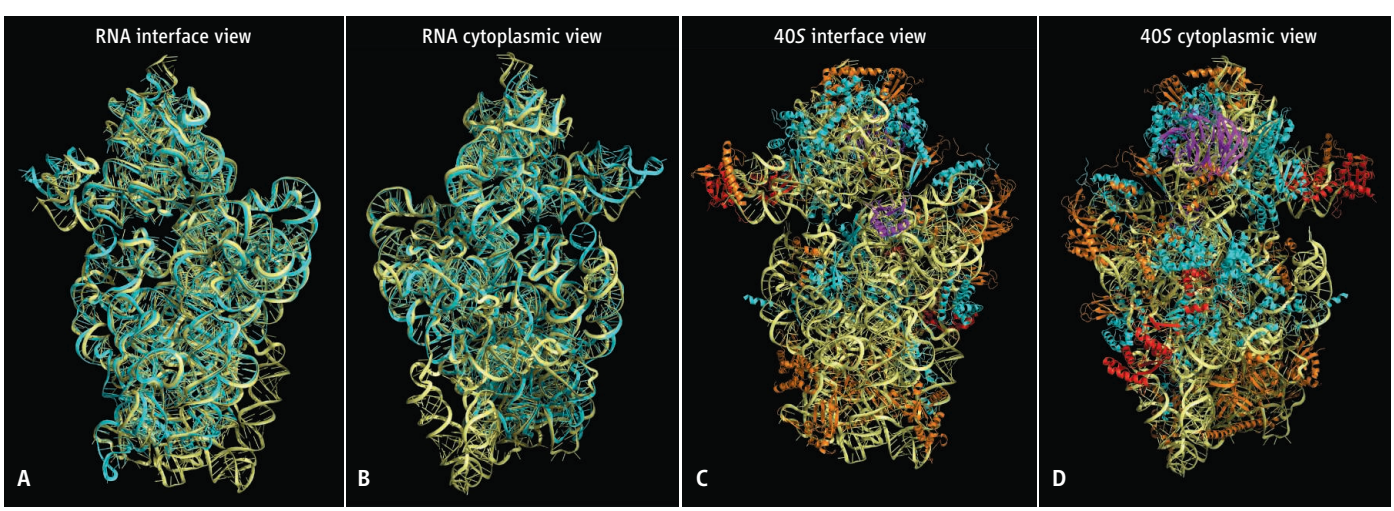

Eukaryotic 40S ribosome. (**A** and **B**) A superposition of eukaryotic 18*S* RNA (*2*) and bacterial 16*S* RNA. (**C** and **D**) Corresponding views of eukaryotic 40*S* (*2*). Proteins with bacterial homologs shown in cyan, those with archaeal homologs in gold, and those unique to eukaryotes in red. Proteins eIF1 and RACK1 are magenta (C and D).

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the eukaryotic translation initiation factor 1 (eIF1) is only 0.25 Å higher than that of the yeast 80*S* structure, it is the most accurate and complete. The authors were able to build a well-refined model from a combination of secondary structure prediction, information about the location of large bulky side chains and zinc ions, and biochemical knowledge. However, even for this structure, the resolution of 3.9 Å suggests that there could still be some errors, especially in the registry of the protein chains.

Functionally, the most interesting finding from the yeast 80*S* structure is that it is in the fully ratcheted state, in which the two subunits have rotated relative to each other. This state is known to be an intermediate in translocation (*11*–*13*). Although partially ratcheted states have been observed crystallographically for the bacterial ribosome (*14*), this is the first high-resolution structure of a fully ratcheted state and provides more detailed information about the disruption and formation of contacts required to translocate transfer RNA (tRNA) and mRNA through the ribosome. However, a proper characterization of the intermediate state in translocation will require a more complete structure with the tRNA and mRNA ligands present, as has been accomplished with cryo-EM in the bacterial case (*12*, *13*).

Because Rabl *et al*. were able to model all the proteins in the 40*S* structure, some general lessons can be gleaned. Eukaryotic ribosomal proteins make extensive contacts with each other, rather than mainly with rRNA, as is the case in their bacterial counterparts. Some features, such as the "beak" of the 40*S* subunit, are extensively remodeled to be the same overall shape as that of the bacterial 30*S* subunit, but are made of proteins rather than RNA. Moreover, some bacterial proteins have been structurally replaced by nonhomologous eukaryotic counterparts. A number of functional mutations could be mapped on the 40*S* subunit, and RACK1 (receptor for activated C kinase), a protein that serves as a signaling scaffold, appears to be a stably bound, intrinsic component of the ribosome. Finally, this is the first structure to reveal the precise location and interactions of initiation factor eIF1 with the 40*S* subunit, thus shedding light on its potential interactions with eIF1A and initiator tRNA.

These two structures, by showing that it is possible to crystallize eukaryotic ribosomes and their subunits despite their potential heterogeneity, have overcome a major stumbling block toward the understanding of eukaryotic translation.

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COMPUTER SCIENCE

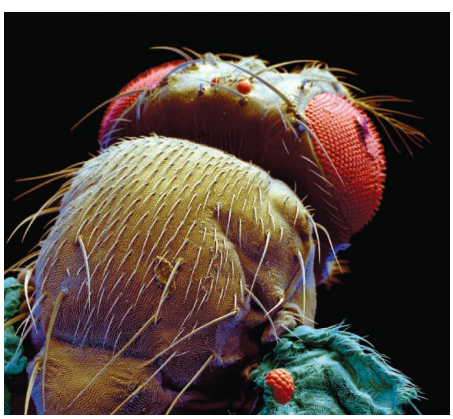
Learning from Nature

The developmental biology of a fly's bristles leads to a better computer network algorithm.

Jeffrey O. Kephart

The tradition of biologically inspired computing extends back more than half a century to the original musings of Alan Turing about artificial intelligence and John von Neumann's early work on self-replicating cellular automata in the 1940s. Since then, computer scientists have frequently turned to biological processes for inspiration. Indeed, the names of major subfields of computer science—such as artificial neural networks, genetic algorithms, and evolutionary computation—attest to the influence of biological analogies.

Recently, Afek *et al*. (*1*) offered an example of how biology can inform computer science. Working in collaboration, computer scientists and molecular geneticists studied how sensory bristles develop in fruit flies (see the figure) and then used what they learned to solve a challenging problem in organizing distributed computer networks. By exploring a biological process, they were able to develop an algorithm, or set of rules that define a sequence of operations, that is more practical than any other produced during decades of work on this problem.



Bristle-based computing. Studying the development of a fruit fly's sensory bristles provided insight into developing a more practical algorithm for organizing networked computers.

These encouraging results are among the latest to emerge from efforts—of varying breadth and depth—to apply biology to computation. Sometimes, these analogies are useful even if applied only broadly. For instance, the term "autonomic computing," coined in 2001 (*2*), conveyed the idea that, in order to cope with a looming crisis in the complexity of managing large-scale computing systems, we needed to imbue them with the ability to manage their own behavior in a manner akin to the human body's autonomic nervous system, which governs functions such as heart rate and pupil dilation. Academia found this vision compelling, and research in the field remains active. So far, however, biology has not provided a blueprint for solutions. A scan of the autonomic computing literature, for instance, reveals that few researchers have seriously attempted to develop computer analogs of the mechanisms employed by the autonomic nervous system, and only a handful have pursued approaches to self-managing computing that are in any way biological.

In contrast, biological structures and processes such as neural networks, molecular genetics, and immune systems have provided more detailed blueprints that, when interpreted judiciously at the right level of abstrac-

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