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Whither ribosome structure and dynamics research? (A Perspective)

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Abstract

As high-resolution cryo-EM structures of ribosomes proliferate, at resolutions that allow atomic interactions to be visualized, this article attempts to give a perspective on the way research on ribosome structure and dynamics may be headed, and particularly the new opportunities we have gained through recent advances in cryo-EM. It is pointed out that single-molecule FRET and cryo-EM form natural complements in the characterization of ribosome dynamics and transitions among equilibrating states of *in vitro* translational systems.

Keywords

cryo-EM; smFRET; time-resolved methods; translation

The recent surge in resolution of single-particle cryogenic electron microscopy (cryo-EM) to the 4-3 Å range and even beyond is about to spur an avalanche of structures of ribosomes modeled in atomic detail. The ribosome structures in this resolution range that have already appeared within the span of just over two years (1–13) give us an idea of what is possible now. The field has never been so exciting as we are now able to study detailed interactions within the ribonucleic protein assembly that are responsible for the stability of the structure of the ribosome, as well as its allosteric dynamic properties. It is a measure of achievement that we are now able, at resolutions ranging from 2.5 to 3 Å, to pinpoint the locations of magnesium ions and rRNA modifications, both instrumental in controlling stability of the rRNA and its interactions with tRNAs and mRNA (6,12).

Once the shape and structure of the ribosome had been revealed through efforts by cryo-EM (14–16) and, in atomic detail, by X-ray crystallography (17–20), the stage was set for a re-interpretation and re-evaluation of a large body of literature accumulated over the decades before, encompassing the results of genetic, biochemical, and biophysical studies. This

evaluation is still in progress and it is also expanding in scale as the ribosome is increasingly seen as a node of crucial importance in the large interaction network of the cell. New structural information is gathered with a view on these multiple interactions with agents that perform regulatory and control functions. Taking advantage of the novel capability of single-particle cryo-EM to retrieve an entire inventory of states from a single sample (e.g., (21–24)), researchers are turning their attention more and more to ribosomes purified from cell extracts, and take the spectrum of states as a snapshot of the protein production in the cell (22–24). However, to what extent the protocols for extraction, purification and cryo-EM specimen preparation allow us to obtain an unbiased description of a sample is still an open question that needs to be addressed with considerable urgency. Without an answer to this question, the results of such studies are difficult to compare with one another, and they will fall short of a quantification for the occupancies of states.

A systematic structural biological approach toward translation will entail an exhaustive description of the ribosome as a processive molecular machine visiting multiple states, with the idea that these states are ordered in a causal way, encompassing the entire workflow of protein synthesis. Even for bacteria, flowcharts of translation such as compiled by Schmeing and Ramakrishnan (25) show many steps characterized by intermediate, relatively long-lived complexes that are formed by a combination of ribosomal subunits, numerous factors, mRNA and tRNAs. This great variety in composition is confounded by dynamic variations in conformations and binding interactions along each pathway, which may split some of the states in the diagram into several sub-states. A complete description of all of these sub-states for a single species alone will already be a tall order. Such a description is most effectively approached by using a defined *in vitro* translation system, though the question to what extent it would be representative of the *in vivo* situation still remains a challenge.

In terms of future research agendas, such comprehensive descriptions may not be required for more than a few representative species since sequence information informs us about any change in structural components that might affect function in a significant way. Thus one issue that could benefit from community consensus would be the choice of the different species to be singled out for this kind of comprehensive structural analysis. What comes to mind, as a minimum set covering representatives of the kingdoms, are *Escherichia coli*, *Haloarcula marismortui*, *Saccharomyces cerevisiae*, *Plasmodium falciparum*, rabbit reticulocyte, human, and wheat germ – because these are model systems for which the process of translation has been characterized to various degrees, and some structures of ribosome complexes in selected stages of translation are already available in the public databases. This list is of course open to debate.

As we attempt to approach an understanding of translation we have to distinguish among several levels of the biological problem: one is the fundamental level, on which the understanding of the polypeptide elongation cycle in *E. coli* informs us about the mechanism of elongation in all other organisms. On that level we already see a broad convergence of results and views, and a trend to go toward inquiries into more subtle details of mechanism, even though the role of EF-G is still controversial. Next there is the kingdom-specific level, on which we strive to characterize and understand in broad strokes the differentiations that make some processes of translation unique, such as initiation and co-translational protein

translocation in eukaryotes. This is an active area of investigation which will particularly benefit from the improved resolution and the ability to resolve heterogeneity in cryo-EM data. Finally, there exists a level on which we wish to know specific mechanisms of regulation and control that are distinct in different genus and families. On that level, particularly because of the role that allosteric mechanisms and ribosome dynamics play, we have only just begun making headway.

It should be mentioned that the path toward a full understanding of translation and its regulation has become more complicated with the discovery of specialized ribosomes in tissues and development (26) and the dependence of ribosome composition on environmental conditions (27). We have come a long way from the naïve picture of a defined, invariant ribosome that is the same in each cell of an organism to one where the ribosome is more or less in flux, as a subset of ribosomal proteins might not be present at a certain stage of development or under certain stress conditions. Much research is needed to find the rationale for this observed variation in composition and its regulation in the cell.

One of the biggest challenges is to gain a better understanding of the ribosome as a dynamic molecular machine. Information on its conformational changes during translation – directly or indirectly – comes from a whole variety of experimental approaches: molecular genetics, rRNA footprint studies, single-molecule fluorescence resonance energy transfer (smFRET), cryo-EM, and X-ray crystallography, to name the most important ones. Of these cryo-EM and smFRET can be singled out as techniques lending themselves to coordinated studies that yield different aspects of the same process from the same sample. In the following I will elaborate on this tenet.

In cryo-EM, as already mentioned above, the fact that three-dimensional reconstructions from distinct classes can be obtained from a given sample means that multiple states of an equilibrating system may be visualized all at once. This offers the opportunity to look at well characterized *in vitro* translation systems and determine the entire inventory of co-existing structures. Although juxtaposition of these structures cannot yield conclusive connecting “story lines,” nor kinetic rate constants related to the putative transitions, this complementary information can be gained by employing smFRET.

Non-equilibrated systems can be analyzed in the same way, by visualizing specimen samples at different time points, and then analyzing how the system evolves over time. Slowly evolving translational systems (on the scale of minutes) have been studied in this fashion (28); however, most reactions of biological interest are too fast (< 1000 ms) to be captured at multiple time points by standard cryo-EM, as it uses the time-consuming step of blotting. For the study of short-lived reaction intermediates in the 10–1000 ms range, time-resolved methods can be employed, which work either by spraying a reactant onto a grid bearing another reactant (29) or by employing a microfluidics chip in a novel mixing/spraying method (30–33).

Early on, smFRET has already greatly contributed to our understanding of the stochastic nature of ribosome dynamics, on the background of structural information that directed strategic placement of the probes and interpretation of the recorded signals (34–40). This

technique allows the dynamic behavior of single molecules to be followed in real time. In addition to other feats, smFRET helped elucidate the Brownian character of the ratchet-like intersubunit rotation and associated changes of the L1 stalk (41–50). Recent advances in the field include multiple-wavelength experiments in which an smFRET signal reporting on the conformational dynamics of the ribosome is recorded simultaneously with one or more fluorescence co-localization signals reporting on the binding/dissociation of tRNAs, factors, and other ligands to the ribosome. In this kind of experiment, for instance, the ratchet-like motion of the ribosome and the arrival or departure of EF-G are reported independently, allowing the synchronization of these events to be gauged (51). Such multiple-wavelength experiments can be expected to provide a much richer description of the way conformational changes of domains are synchronized with events of binding and dissociation of tRNAs and factors. Another advancement with great potential for investigating the dynamics of processes during translation is *Single-Molecule Polarized Fluorescence Microscopy*, which is capable of reporting on domain rotations in real time and has been used by the groups of Yale Goldman and Barry Cooperman to study rotations of EF-G domains during mRNA-tRNA translocation (52).

A drawback of many studies using smFRET is that the exact geometry with which the FRET donor- and acceptor fluorophores are placed within the structural framework of the molecule cannot be ascertained for the conditions under which the experiment is performed. In addition, dynamic information is confined to the observation of changes in the distance between the fluorophores, while no information is available on the changes of the structures as a whole. For these reasons it will be desirable in the future to coordinate smFRET with cryo-EM studies of the same sample (53, 54). A certain limitation in these studies is presented by the finite time window in smFRET which places a lower bound on the time interval that can be resolved (55). Translocation poses a particular challenge as a process going through multiple short-lived intermediates (50,54,56).

Finally, it should be mentioned that, despite the immense size of the ribosome, all-atom computational simulations of its dynamics with explicit water modeling are already underway. These simulations can offer insights on how key events such as the accommodation of the A-site tRNA or mRNA-tRNA translocation may be realized. Computational power of this scale was initially available only to researchers at institutions with vast resources such as the Lost Alamos National Laboratories (57), but now more widely available thanks to the acceleration of processors and improved access to large-scale resources and cloud computing. For the first time these simulations allow us to appreciate features of the ribosome’s architecture that are instrumental in defining its functionally tailored energy landscape (58–60). While biological insights might not be readily gained at this point, it is of considerable interest that models of system with this complexity already approach a degree of perfection that allows prediction of experimentally observed dynamic trajectories.

In conclusion, recent advances in cryo-EM have opened up exciting new avenues in the study of structure and dynamics of the ribosome. Particularly promising is the pairing of cryo-EM of equilibrating translational systems with real-time single-molecule FRET of the same sample. Much research still lies ahead, given the dominating role of protein synthesis

in the cell, but it will predictably be more narrowly focused for fundamental insights on a small number of model organisms, selected by consensus of the community. The increased resolution and the ability to disentangle the spectrum of conformational states will benefit the systematic exploration of mechanisms pertinent to regulation and control in eukaryotes, most importantly those relevant to human health.

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