The structure of the ribosome – short history

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Summary

Ribosomes, which are "the heart of the protein biosynthesis" have been the focus of structural studies for more than 50 years. The reconstitution of some of the morphological features of the ribosome was performed many years ago. In the past few years, high-resolution structures provided molecular details of different intermediates in ribosome-mediated translation. Together, these studies have revolutionized our understanding of the mechanism of protein biosynthesis. This success depended strictly on the advances in biochemical, biophysical and genetic studies and macromolecular crystallography that have been made during last decades.

Key words:
ribosome's structure, protein biosynthesis, X-ray, cryo-EM.

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1. Introduction

The ribosome is composed of two subunits that work together to carry out mRNA-directed polypeptide synthesis. This process involves a highly dynamic interplay of two ribosomal subunits with each other and numerous cellular factors. Our understanding of protein biosynthesis is most advanced for bacteria which contain 70S ribosomes composed of a small (30S) and a large (50S) subunit. The activity of the ribosome involves initiation, elongation, termination and recycling step. The ribosome

adopts many different functional states during each of the above steps. Understanding the complicated details of translation, therefore, requires, in addition to biochemical data, high resolution structures of each of the functional states of the ribosome. Our understanding of ribosomal structure has proceeded from the early reconstructions of the shapes of the two interacting subunits, to the current atomic-resolution structures of the prokaryotic 70S ribosome and of its large and small subunits captured in various functional states. Our intention is to present in this review how our knowledge about the ribosome's structure evolved, starting from its discovery untill nowadays.

2. It started from the mitochondria…

The beginnings of the long and continuous discovery of the ribosomes lie in an excellent work with cell fractionation in the 1930s and 1940s performed by Albert Claude, the 1974 Nobel Prize laureate in Physiology or Medicine. To realize the knowledge about cells in those days, let's see what Claude said on December 12th 1974 during his Nobel lecture: "*Until 1930 or thereabout biologists, in the situation of Astronomers and Astrophysicists, were permitted to see the objects of their interest, but not to touch them; the cell was as distant from us, as the stars and galaxies were from them*". The primary instrument of investigation for classical cell biologists – the light microscope, was physically incapable of resolving a cell's interior details. The particulary components of the cell were first seen in 1941 but were not recognized yet. By means of newly developed high-speed centrifugation, the cytoplasm no longer appeared as neverending space full of unknown substances, but as a powerfull space in which the unknown substances showed up, waiting to be isolated, purified and characterized. The subcellular fragments could be obtained by many scientists by rubbing cells in a mortar, and further subjection to multiple cycles of sedimentations, washings and resuspensions. In addition to the nucleus, which was the most prominent feature of eukaryotic cell, mitochondria were also visualized in such way. In fact, mitochondria were detected under the light microscope as early as 1894, but despite extensive investigation by microscopy in the course of the following 50 years, no progress was achieved in this field. Finally, in 1940s, the staining properties of mitochondria led to the conclusion that they contained ribonucleic acids and thus put them as an object of new studies.

3. … then the microsomes appeared…

Albert Claude, who was working with chicken embrions' mitochondria, noticed that they contained relatively big fraction of pentose nucleic acids and a fraction of smaller particles. He first called them "small granules" and later "microsomes" (1)

and he presumed that they could be engaged in anaerobic glycolysis. Since Claude's findings, others started to perform more detailed fractionactions of cells. It was noticed that eukaryotic "microsomes" were heterogenous in size as well as in composition. It took a decade to obtain purified "microsomes". Almost at the same time Howard Schachman, Mary Petermann and John Littlefield noticed that RNA:protein content of the microsomes was 1:1 (refered in (2)). Later Mary Petermann observed another distinct granules in her material. These were considerably smaller than the average microsomes (in range of 20 nm) and very rich in ribonucleic acids. Petermann refered to them as "macromolecules".

The situation began to change with the use of electron microscopy. In 1955, Philip Siekevitz and George Palade (student of Claude and the 1974 Nobel Prize co-laureate in Physiology or Medicine) showed that Claude's "microsomes" were fragments of endoplasmic reticulum (3) (as postulated by Claude in 1948). Moreover, on the surface of endoplasmic reticulum dense granules were present (Fig. 1). To find out more about the "microsomes", Palade and Siekevitz started an integrated morphological and biochemical analysis of the secretory process in the guinea pig's pancreas and liver (4). In fact, the research area of the "microsomal" function was quite distinct from studies of its structure. The history of the functional research on "microsomes" is presented in (5) and our intention is to present how the knowledge of the ribosome structure evolved. We just want to point out that the first group of scientists who connected the "microsomes" with protein biosynthesis was Paul Za-
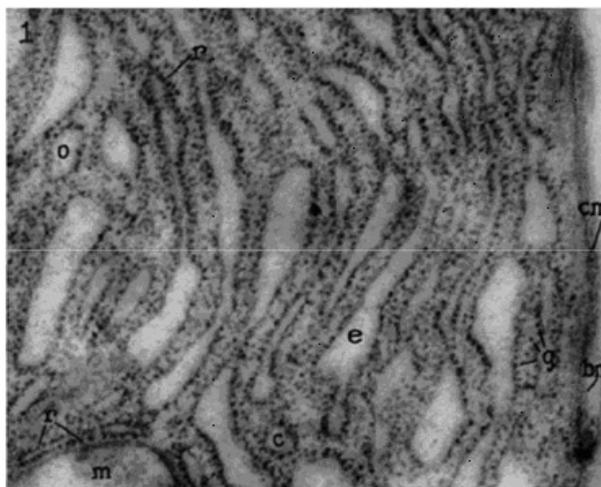

Fig. 1. George Palade's "Electron micrograph of a limited field in the basal region of an acinar cell of the pancreas (rat)" (3).

The picture presents: the cell membrane (cm), part of mitochondrium (m), elongated (e), oval (o), and circular (c) profiles of the endoplasmic reticulum, free "microsomes" (g) and "microsomes" bound to reticulum (r).

mecnik's group. Zamecnik started his work on protein biosynthesis in 1945, first by introducing radioactively labelled amino acids into rat livers and then observing that the incorporated isotopes were predominantly present in the microsomal fraction (6). He also started to isolate and identify components necessary for protein biosynthesis. By 1953 he had succeeded in making the first cell-free system capable of carrying out new peptide bond formation using ^{14}C-labelled amino acids (6,7).

4. … and finally, the ribosome!

In 1950s, the ribosomal RNA was generally assumed to provide the template upon which amino acids were assembled into protein chain. To put attention to the role of ribosomal RNA, term "ribosome" was first proposed by Richard Brooke Roberts in 1958, at a meeting of the Biophysical Society (it was at this meeting that George Palade called Mary Petermann the "mother of the particles"). The word "ribosome" itself origins from ribonucleic acid and Greek *soma*, meaning body.

Around 1960s, scientists already knew how to prepare active ribosomes from many organisms and started to explore their physico-chemical properties. In 1956, Howard Schachman and Fu-Chuan Chao isolated stable ribosomes with a sedimentation coefficient of 80S from yeast extracts, and noticed that they dissociate into two portions of 60S and 40S. Their analyses indicated that the 80S particles were a ribonucleoprotein containing about 42% RNA and 58% protein (8). One year later Mary Petermann and Mary Hamilton were able to characterize 77.5S ribosomes from calf and rat liver, and noticed that they contained 40% of nucleic acids (9). First prokaryotic ribosomes were characterized in this way (70S particles dissociated in 50S and 30S particles) in 1958 by Alfred Tissieres and James Watson with *Escherichia coli* as a source of the particles (10).

First ribosomal component characterised and purified was ribosomal RNA. In 1959, Paul Ts'o separated rRNAs from 74S ribosomes isolated from pea epicotyls, into two fractions: 28S and 18S rRNA (11). *E. coli* ribosomes served as a source of separation and characterisation of 23S and 16S rRNAs by Alexander Spirin (12) and Charles Kurland (13) basically at the same time. And finally in 1963, 5S rRNA was identified as a native part of mature ribosomes (14).

When it comes to the ribosomal proteins, they remained a mistery till the beginning of 1960s. One should mention here excellent work in study of ribosome's protein composition of Jean-Pierre Waller (15), David Elson (16) and Pnina Spitnik-Elson (17). In 1961 in his PNAS paper, Waller wrote that all ribosomal proteins most often had two amino acids at their N-terminus: methionine and alanine. This led to conclusion that ribosomal proteins are a special class of basic proteins that "quite possibly serves the role of maintaining ribosomal RNA in a suitable conformation for protein synthesis" (15). One of the first identified proteins characterized in more details was so called A-protein (at present time called L7/L12). This work was done in

1967-1970 in Wim Möller's laboratory (18). Möller showed, that A-protein was an integral part of 50S subunit and also discussed the possibility that this protein is involed in peptide bond formation.

The most impressive fact, that enabled more specific studies, like molecular interactions within and with the ribosome, was that *E. coli* ribosome became first organelle whose RNAs (5S rRNA as the first (19)) and proteins were completely sequenced. Since that time rapid and continous increase in ribosomal data can be observed. According to The Comparative RNA Web (CRW) Site, in 1980s, there where only two sequences of 16S rRNA available that constitues only 0.03% of 7.000 16S rRNA sequences available 20 years later (20). It should be also mentioned that progress was noticed not only in the number of sequences available but also in the precision of its reading (in 1980s, only 80% of the sequence was correct). This led the scientist to explore molecular details of ribosome's function. The great progress could not be achieved without the development of many usefull methods for the ribosome's studies, like: *in vitro* reconstitution of active large ribosomal subunits from its purified components, mutational studies, cross-linking or cryo-electron miscroscopy and finally crystallization of the ribosome. Especially the last two techniqes appeared to be the most powerfull tool to understand ribosomal structure and function.

5. Cryo-electron structures of the ribosome

Single-particle cryo-electron microscopy has two obvious advantages: there are no size limitations, and the complex does not need to be ordered in an array or to be tumbled at any given rate (21). Electron microscopy played an important role in the discovery of the ribosome and, until recently, it was the source of most of what was known about ribosome's morphology, the location of the active sites and the positions of its components. First models of small and large subunits were made in 1970s from EM images of negative-stained specimens (22). Early low-resolution cryo-EM reconstructions of the bacterial 70S ribosome (for example (23)) revealed distinct morphological features, such as the central protuberance, and L1 and L7/L12 stalks in the 50S subunit. First detailed three-dimensional images of the ribosomes were provided in 1995 by Joachim Frank and Hogler Stark groups (24-26). Other cryo-EM maps of the ribosome were obtained capturing various stages in the protein synthesis. The complexes were either biochemically stable or trapped by antibiotics which arrest the translation cycle at specific steps. These include complexes of the bacterial 70S ribosome with tRNAs bound to A-, P-, and E-sites (27,28), the mRNA tunnel through the 30S subunit (25), as well as the ribosome with elongation factors bound (28-31). Morover, single-particle cryo-EM studies of the eubacterial ribosome, enabled the phenomenological observation of conformational changes associated with ribosome's function ((32), which was the first observation made

using cryo-EM of large conformational changes – a ratchet-like inter-subunit reorganization in the ribosome accompanying translocation). The ribosomal dynamics is observed through systematic comparison of differenet models obtained by cryo-EM and X-ray studies. For example, in 2003 an atomic model of bacterial ribosome was fitted into the cryo-EM reconstructions of a pretranslocational (pre) and posttranslocation (post) 70S ribosome by Haixiao Gao group (33). This study represented a significant advance as it helped to identify conformational changes associated with one of key steps of translocation, the ratcheting step. Recently, a systematic comparison of atomic models fitted into the cryo-EM reconstructions of two ribosomes stalled in elongation was performed: one stalled in the absence of EF-G (a prestate ribosome) (34), and the other in the presence of the SecM nascent peptide stalling sequence in the polypeptide exit tunnel (35). This comparison enabled the elucidation of molecular mechanism underlying SecM-induced elongation arrest in the ribosome (36).

Structural information from cryo-EM maps of eukaryotic ribosomes is now available for yeast (37), *Trypanosoma cruzi* (the kinetoplastid protozoan pathogen that causes Chagas disease) (38), eukaryotic green alga *Chlamydomonas reinhardtii* (39), and most recently for mammalian 80S ribosomes (40). Structural differences between rabbit 80S and *E. coli* 70S ribosomes could be interpreted in terms of ribosomal RNA expansion segments in the 18S and 23S RNA (41). The EF-G eukaryotic homologue EF2 was mapped by analysing the structure of an 80S/EF2/sodarin complex (42) and additionaly binding of a hepatitis C virus IRES element to a human 40S subunit has been studied (43). It was also possible to identify a new scaffold protein, RACK1 on the head of the 40S subunit, in the immediate vicinity of the mRNA exit channel (44).

6. Crystal structures of the ribosome

It has been clear for decades that X-ray crystallography can provide high-resolution structures for macromolecules, but its revelance to the ribosome was uncertain for a long time. The reason for this was that for many years there were no ribosome's crystals available, first because of its size, and second because the noncrystallographic symetry (proven to be so important in determining the structures of comparably large assemblies like viruses) does not exits in the ribosome. First potentially useful crystals were not reported until 1981, when Ada Yonath presented the structure of large ribosomal subunit proteins from *Bacillus stearothermophilus* (Fig. 2) (45). In the late 1980s ribosome's crystals were obtained that diffracted to moderately high resolution. But the first work that was marked as a milestone was performed in 1991, when Yonath group obtained diffraction below 3 angstroms from crystals of the 50S subunit (46), which means that atomic resolution structure of the ribosome was possible to explore. After almost 20 years of continued effort, atomic resolution
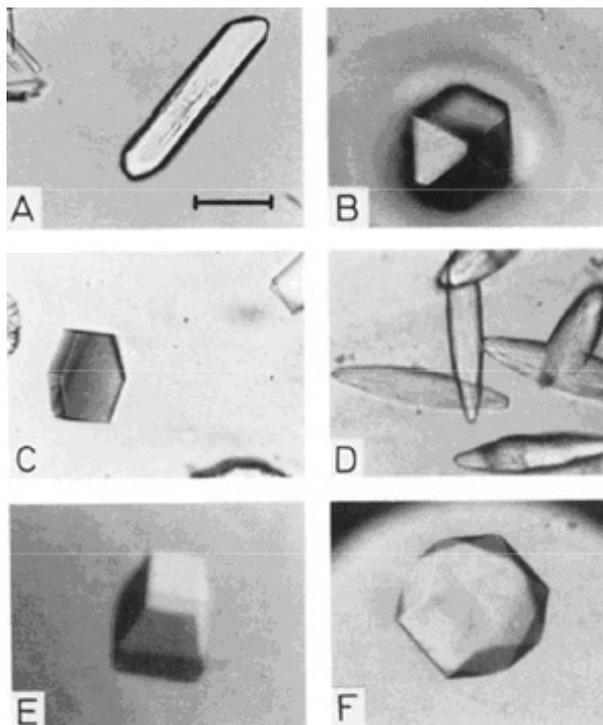
Fig. 2. Ada Yonath's crystals of the ribosomal proteins (A-F) (45).
The bar indicates a length of 0,2 mm.

was achieved for crystals of large ribosomal subunit from *Haloarcula marismortui* (47) and *Deinococcus radiourans* (48) and of small subunit (49) as well as the whole ribosome from *Thermus thermophilus* (50). The structure of small subunit (ssu) is available in the Protein Data Bank (51) in three most important entries: 1fka (stucture of functionally activated ssu, resolved in 2000 by Schluenzen et al. (52)), 1fjf (for the native structure of 30S, by Wimberly et al. (49)) and 1fjg (for 30S in complex with antibiotics: streptomycin, spectinomycin, and paromomycin, by Carter at al. (53)). The structure of large ribosomal subunit is available in PDB entry 1ffk. The latter one was resolved by Ban et al. in 2000 (47). None of these could exist without long-standing efforts of many scientist, whose names should be remembered because our knowledge is based on the past.

After few more years, we posses even more detailed crystalographic studies of the ribosomes. Recently obtained all-atom crystals of 70S ribosome functional complexes give a detailed description of how the ribosome interacts with mRNA and tRNA substrates (Fig. 3) (54-57). The 3.5 angstroms structures of *E. coli* ribosomes provided a detailed view of the interface between small and large ribosomal sub-
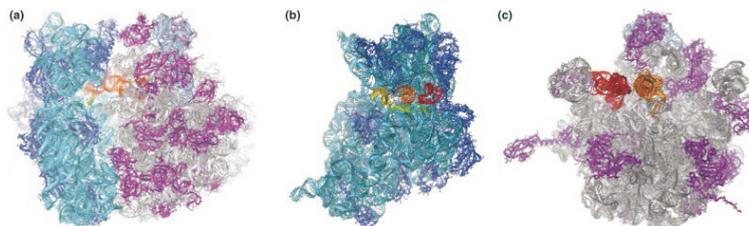
Fig. 3. Structure of 70S functional complex (54).

(a) 70S functional complex containing P- (orange) and E-site (red) tRNAs and mRNA (green). 23S rRNA is shown in grey, 5S rRNA is shown in grey–blue and the large (L)-subunit proteins are shown in purple. 16S is shown in cyan, and the small (S)-subunit proteins are shown in blue.

(b) 30S subunit, viewed from the subunit interface. The ASL of A-site tRNA (yellow), P- (orange) and E-site (red) tRNAs and mRNA (green) are all visible.

(c) The 50S subunit viewed from the subunit interface. The P- and E-site tRNAs are shown.

units and the conformation of a peptidyl transferase center in the context of intact ribosome (58). Other available important crystal structures are for example: functional complexes of *T. thermophilus* 30S subunit bound with an mRNA mimic (59), large subunits with the ribosomal recycling factor (60) or with the release factors (61,62). All of currently available crystal structures are of ribosomes from prokaryotic organisms, in most cases adapted to extreme environmental conditions, because these are more suitable for crystallization. Yet, there are no crystal structures of eukaryotic ribosomes available. 80S ribosomes are more complex and generate more difficulties in research. Owing to the high level of ribosomal core conservation between 70S and 80S, more detailed studies can be most likely superimposed from 70S to 80S system.

7. Conclusions

Biochemists interested in protein biosynthesis have long taken as axiomatic a fact that the mechanism of the ribosome's action will not be fully deciphered untill three-dimensional structure is understood in atomic details. For that reason, much of the work done on the ribsomes since 1960s has been directed to its structure.

Although the core aspects of protein biosynthesis are highly conserved across all three kingdoms, some, such as the initiation of protein synthesis, differ significantly. So far, only cryo-EM studies of eukaryotic ribosomes have been successful. High-resolution structural studies of eukaryotic ribosomes and, most importantly, complexes of the 40S ribosomal subunit captured in the act of initiation in complex with initiation factors, tRNA and mRNA have not yet been accomplished. Structural insights into this aspect of protein synthesis will be of particular interest for the next years because of its crucial role in regulation of translation.

Acknowledgments

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