ABSTRACT
Ribosomes are the sites of protein synthesis. The name of these tiny organelles reflects their high content of one type of ribonucleic acid, ribosomal RNA (rRNA), but each one also includes more than 50 proteins. Structurally, a ribosome consists of two subunits, one about half the size of the other. The large and small subunits are made separately in the nucleolus, a spherical body inside the nucleus. Once produced, the large and small subunits exit the nucleus separately, and then come together in the cytoplasm. These are tiny granules composed of RNA and protein. They synthesize proteins from amino acids, using RNA as the template. When present in free units or in small clusters in the cytoplasm, the ribosomes make proteins for use within the cell. Ribosomes are also found on the outer surface of rough endoplasmic reticulum.

KEYWORDS: Ribosomes, Discovery of 30S and 70S, Action of Antibiotics on Ribosomes.

INTRODUCTION
Some ribosomes are attached to the outer surface of the nuclear membrane and to an extensively folded membrane called the endoplasmic reticulum. These ribosomes synthesize proteins destined for specific organelles, for insertion in the plasma membrane, or for export from the cell. Other ribosomes are “free” or unattached to other cytoplasmic structures. Free ribosomes synthesize proteins used in the cytosol. Ribosomes are also located within mitochondria, where they synthesize mitochondrial proteins.\(^1\)

Historical Perspectives of Ribosomes
Ribosomes are the heart of the protein biosynthesis and have been the focus of structural studies for more than seven decades. 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.

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 (Svedberg unit which measure the rate of sedimentation) 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.[2]

The process started from 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 particularly 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 never ending space full of unknown substances, but as a powerful 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. Albert Claude, who was working with chicken embryos, 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”. In 1955, Philip Siekevitz and George Palade showed that Claude’s “microsomes” were fragments of endoplasmic reticulum. Moreover, on the surface of endoplasmic reticulum dense granules were present. 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. 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, 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 Zamecnik’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. 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 14C-labelled amino acids. Finally, 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. 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. One year later Mary Pettermann and Mary Hamilton were able to characterize 77.5S ribosomes from calf and rat liver, and noticed that they contained 40% of nucleic acids. First prokaryotic ribosomes were characterized in this way in 1958 by Alfred Tissieres and James Watson with Escherichia coli as a source of the particles. 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.\textsuperscript{[12, 57]} \textit{E. coli} ribosomes served as a source of separation and characterisation of 23S and 16S rRNAs by Alexander Spirin,\textsuperscript{[13]} and Charles Kurland,\textsuperscript{[14]} basically at the same time. And finally in 1963, 5S RNA was identified as a native part of mature ribosomes.\textsuperscript{[15-54-56]} When it comes to the ribosomal proteins, they remained a mystery till the beginning of 1960s. One should mention here excellent work in study of ribosome’s protein composition of Jean-Pierre Waller,\textsuperscript{[16]} David Elson,\textsuperscript{[17]} and Pnina Spitnik-Elson.\textsuperscript{[18]} 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”. This led the scientist to explore molecular details of ribosome’s function. The great progress could not be achieved without the development of many useful 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 microscopy and finally crystallization of the ribosome. Especially the last two techniques appeared to be the most powerful tool to understand ribosomal structure and function.

\textbf{Ribosomes and Life}

Ribosomes are large macromolecular assemblies consisting of approximately two-thirds by mass of RNA, with the rest being proteins. By around 1980, several large complexes had been crystallized. The ribosome, however, was considerably larger than any of these; moreover, it was not even clear initially whether ribosomes in the cell were identical or consisted of a mixture of subtypes that might be specialized for different messages. A few years later, the crystallization of both the small (30S) subunit and the entire 70S ribosome from \textit{Thermus thermophilus} was also reported.\textsuperscript{[19, 53]} Thus, by the end of the 1980s, both subunits and the entire ribosome had been crystallized. These early crystals were not of sufficient quality to yield a high-resolution structure. However, after an extensive search involving many different species, the development of synchrotron radiation sources to provide intense beams of X-rays\textsuperscript{[20]} was crucial to provide sufficient signal from these weakly diffracting crystals. Another advance was the development of cryocrystallography as a general tool to minimize radiation damage from these intense X-ray beams,\textsuperscript{[21]} which was quickly adapted for data collection on ribosomal crystals.\textsuperscript{[22]} Advances in computing, detectors and crystallographic software were also essential. Nevertheless, despite these
advances, little progress was made through most of the 1990s in obtaining a structure even at the modest resolution of 6–10Å that should have been technically feasible by that time. In any case, for the first time, right-handed helical density corresponding to A-form helices were observed in electron-density maps of a ribosomal subunit, demonstrating a feasible approach to initiating phasing for such large complexes.\[23, 48-52]\n
\[23\]

**Fig 1: Details of Ribosomal Subunits** [1]

**Nucleoli and Formation of Ribosomes**
The nuclei of most cells contain one or more highly staining structures called nucleoli. The nucleolus, unlike most other organelles discussed here, does not have a limiting membrane. Instead, it is simply an accumulation of large amounts of RNA and proteins of the types found in ribosomes.\[24\] The nucleolus becomes considerably enlarged when the cell is actively synthesizing proteins. Formation of the nucleoli (and of the ribosomes in the cytoplasm outside the nucleus) begins in the nucleus. First, specific DNA genes in the chromosomes cause RNA to be synthesized. Some of this is stored in the nucleoli, but most of it is transported outward through the nuclear pores into cytoplasm.\[25,26\]

**Ribosome and Distorted tRNA**
The bacterial stringent response links nutrient starvation with the transcriptional control of genes. This process is initiated by the stringent factor RelA, which senses the presence of deacylated tRNA in the ribosome as a symptom of amino-acid starvation.\[27\]

**Translation**
Translation occurs in a structure called the ribosome, which is a factory for the synthesis of proteins. The ribosome has a small and a large subunit and is a complex molecule composed of several ribosomal RNA molecules and a number of proteins.\[28-30\]


Antibiotics and Ribosomes

Natural or synthetic compounds that either Natural or synthetic compounds that either kill (bactericidal) or inhibit growth (bacteriostatic) of bacteria (or other microorganisms).\cite{31,32,47}

Since ribosomes are essential for life, they make attractive targets for antibiotic drugs. Of course, you need to be careful not to attack our own ribosomes; otherwise you would kill yourself along with the infection. Fortunately, bacterial ribosomes have many small differences from our own ribosomes, so there are many antibiotic drugs that specifically attack 70S ribosomes.

The ribosome is a major bacterial target for antibiotics. Drugs inhibit ribosome function either by interfering in messenger RNA translation or by blocking the formation of peptide bonds at the peptidyl transferase centre. These effects are the consequence of the binding of drugs to the ribosomal subunits. Various mechanisms, including enzymatic detoxification, target alteration and reduced accumulation are involved in bacterial resistance to protein synthesis inhibitors. The fact that some positions in rRNA participate in the binding of antibiotics belonging to distinct families explains why bacteria have developed mechanisms that can lead to cross-resistance.\cite{33-38}

Antibiotics that bind selectively to bacterial or protozoal ribosomes are of great clinical significance due to their ability to treat infectious diseases without compromising the host.\cite{39}

The most effective antibiotics used in clinical treatment exploit subtle differences between distinct locations within the functional sites of prokaryotic and eukaryotic ribosomes. On the other hand, compounds such as sparsomycin.\cite{40} and pactamycin,\cite{41} which are known to interact with the ribosome with universal specificity, have been reported as potential antitumor drugs.\cite{42-46}

CONCLUSION

The purpose of this review is to highlight not only discovery of structural biology of ribosome but also various aspects of ribosome with respect to historical perspectives, it’s components, and their vital role in life. Ribosome is the unit of life on which several drugs are having positive as well as negative effect. For further research in molecular and cell biology ribosome would be the best platform for young researchers.
ACKNOWLEDGEMENT

Authors are grateful to Dr. Venkatraman Ramkrishnan (Nobel Prize in Chemistry 2009) and his entire team of MRC Laboratory of Molecular Biology, Cambridge, UK for making their research and references easily accessible, without this we couldn’t be able to touch such complex issues and perspectives of ribosome with simplicity and ease.

REFERENCES

6. Rheinberger HJ. Protein synthesis and ribosome structure. Translating the genome, Eds. Nierhaus KH, Wilson DN. WILEY-VCH Verlag GmbH & Co. KGaA,Weinheim. 1-52,


50. Ogle JM, Murphy FV. IV, Tarry MJ and Ramakrishnan V. Selection of tRNA by the ribosome require a transition from an open to a closed form. Cell. 2002; 111: 721-732.


