

# Ribosome biogenesis and ribosome therapy in cancer cells

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## Abstract

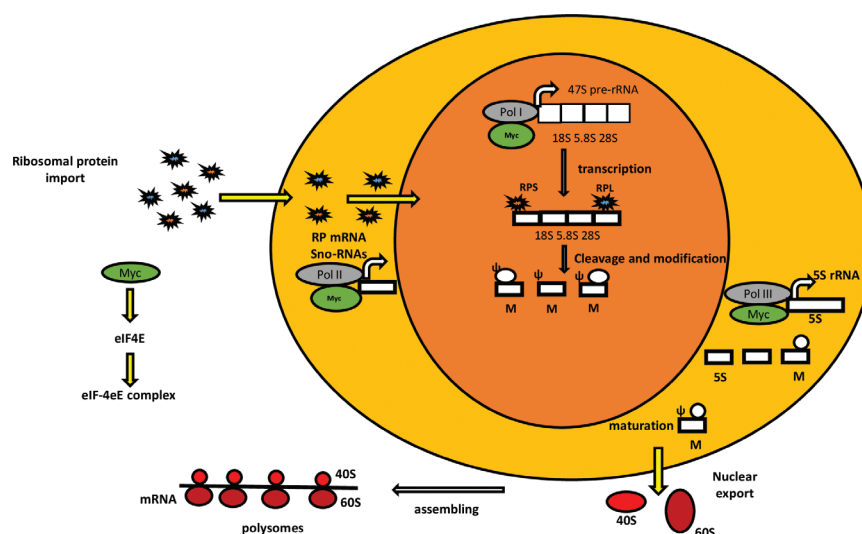
**Introduction:** The process of protein synthesis is a vital process for all kingdoms of life. The ribosome is a ribonucleoprotein complex that reads the genetic code, from messenger RNA (mRNA) to produce proteins and to tightly regulate and ensure cells growth. The fact that numerous diseases are caused by defect during the ribosome biogenesis is important to understand this pathway.

**Materials and methods:** We have analyzed the literature for ribosome biogenesis and its links with different diseases which have been found.

**Results and discussion:** We have discussed the key aspect of human ribosome biogenesis and its links to diseases. We have also proposed the potential of applying this knowledge to the development of a ribosomal stress-based cancer therapy.

**Conclusion:** Major challenges in the future will be to determine factors which play a pivotal role during ribosome biogenesis. Therefore, more anti-cancer drugs and gene therapy for genetic diseases will be developed against ribosomal biogenesis in the coming years.

### Graphical abstract:



## Keywords

ribosomal biogenesis, ribosomal protein processing, ribosome and cancer, cancer therapy, inhibition of ribosome biogenesis.

## Introduction

The huge nanomachine called ribosome is known to be responsible for translation of the genetic information from mRNA into amino acid sequence of proteins in all living organisms. The ribosome consists of two subunits; with small subunit 40S harboring the decoding center and large subunit 60S containing the peptidyl transferase activity. Each subunit comprises ribosomal RNA and ribosomal protein. In a eukaryotic organism, the assembly of ribosomal proteins with pre-rRNA occurs through a sophisticated maturation pathway, which originates in the nucleolus and is finalized in the cytoplasm (Bohnsack and Bohnsack 2019). The maintainance of functionally sufficient ribosome is one of the activities, which is demonstrated in living cells, where 60% of the entire cell transcript is expended on rRNA synthesis (Warner 1999). It is known that for ribosome biogenesis, three RNA polymerases are required; the Pol I and Pol III are mainly necessary for pre-rRNA synthesis, and 50% of Pol II is required for production of mRNA for ribosomal proteins. Due to this high energy, ribosome formation is tightly regulated according to the cell proliferation; considering several conserved regulatory pathways, including a target of Rapamycin complex 1 (TORC1), MYC and p53 (Loewith and Hallm 2011; de la Cruz et al. 2018; Piazzini et al. 2019). An impairment of this regulatory network can cause cancer and neurodegeneration diseases (Mills and Green 2017; Aspesi and Ellis 2019; Bohnsack and Bohnsack 2019; Farley-Barnes et al. 2019; Penzo et al. 2019). For biogenesis of eukaryotic ribosome, is required the synthesis and assembly of 18S rRNA (for 40S ribosomal subunits) and 5S, 508S and 25S rRNA (yeast) or 28S rRNA (mammals) for 60S subunits, as well as 80 ribosomal proteins. This process is very coordinated by plethora proteins, which act as assembly factors (auxiliary or matured factors), including enzymes, such as methyl-transferase, RNA helicase, ATPase and GTPase (Kressler et al. 2010; Sloan et al. 2017). For cell growth and cell division, the ribosome synthesis is very important, and assembly must take place efficiently and with high fidelity. In yeast, for example, more than 200 assembly factors and 77 small nuclear RNAs (snoRNAs) are shown temporarily to be associated with newborn ribosomes, which facilitate these processes. In eukaryotes, more than 500 assembly factors and 300 snoRNAs were found (Lestrade and Weber 2006; Piekna-Przbylska et al. 2007; Tafforeau et al. 2013). For human health, it is important to understand ribosome biogenesis, because ribosome function is linked with cell proliferation, and

dysregulation of this process has profound consequences (Teng et al. 2013).

Now ribosomal proteins are re-appreciated more than structural glue: over half of ribosomal proteins are shown to be essential, and some are shown to be involved in the catalytic activity (Schultze et al. 1982). Also, the ribosomal protein/RNA mass ratio increases along with organismal complex: from ~1:2 in bacteria to ~1:1 in higher eukaryotes (Melnikov et al. 2012), which is evidence for specialized function of some ribosomal proteins (Sulima et al. 2017).

In ribosomal proteins, eukaryotes and prokaryotes are shown to have specific tails extending from their globular domains; several of these extensions protrude deep into the rRNA. Most of these tail extensions thread across the surface of subunits and play a pivotal role in bringing rRNA domains together. Also there are extra sequences embedded in eukaryotic rRNA, known as expansion segment (ES). The ES cluster may contact eukaryotic specific ribosomal protein extensions, suggesting that they have coevolved (Anger et al. 2013).

## Materials and methods

To make analysis of ribosome biogenesis and ribosome therapy for cancer diseases, we used different literature sources. Most of the papers describe clinical and animal studies, when it is shown that ribosomal proteins are responsible for different diseases. Also, small molecules are synthesized by bacteria or fungi who have an ability to inhibit eukaryotic 80S ribosome synthesis. Based on the time of publication of papers, most of the selected studies were published in the period of 2015-2021.

## Results and discussion

### Ribosomal protein synthesis and import to nucleus

The ribosomal proteins are facilitated by transporters, which recognize their nuclear localization signals (NLSs) (Bange et al. 2013). Most of NLSs imported into nucleus will bound to the  $\beta$ -karyopherins Kap123, a HEAT (Huntingtin, elongation factor 3, protein phosphatase 2A, and target of rapamycin 1) repeat-containing protein (Rout et al. 1997). The Kap123 is known to be nonessential protein; but other  $\beta$ -karyopherins, such as Kap108 and Kap121, have an excessive role during the import of ribosomal proteins (Rout et al. 1997). Exactly

what abilities  $\beta$ -karyopherins have to recognize their ribosomal proteins remains unclear. Specific ribosomal proteins required a special system to be imported to the nucleus, for example, in yeast, there is nonessential symportin *Syo1*, which has the ability to associate with the  $\beta$ -karyopherin *Kap104*; this complex facilitated import of ribosomal protein *RPL5/uL18* and *RPL11/uL5* (Kressler et al. 2012). Complex *Syo1-L5/uL18-L11/uL5* in the nucleus is shown to be released by *Kap104*, after interacting with *Ran-GTP*. This interaction is concomitant with the binding of 5S pre-rRNA (Kressler et al. 2012). In yeast, several factors are shown to participate and to promote recruitment of specific ribosomal proteins into preribosomal particles. It is thought that *Rrb1* bind ribosomal protein *L3/uL3* and facilitates the stable assembles (Kressler et al. 1999). But other factors, such as *Rpf2*, *Rrs1* and *Rrb1*, are shown to make very weak associations with preribosomal particles (Iouk et al. 2001; Schaper et al. 2001). The function of *Sqt1* factor is similar with that of *Rrb1*; the *Sqt1* is a high suppressor of dominant-negative C-terminal truncated mutants of ribosomal proteins *L10/uL16* (Eisinger et al. 1997). Another specific factor is *Yar1*, which has an ability to interact with free ribosomal protein *S3/uS3*; after interaction, the complex between *Yar1-S3/uS3* is imported into the nucleus. Once there, *Yar1* seems to assist the proper assembly of *S3/uS3* into pre-40S ribosomes, but it is a very weak interaction with other pre 40S particles (Koch et al. 2012). Other factors, such as trans-acting factors *Ltv1* and *Enp1*, might play a pivotal role (Schäfer et al. 2006). The interaction between C-terminal domain of *S3* and *Ltv1*, as well as between *Yar1* and *Ltv1*, provides docking for *S3/uS3* to pre-40S ribosomal particles (Ghalei et al. 2015). After the *Yar1* is released, it make the N-terminal domain available to interact with other neighbor ribosomal protein particles (Holzer et al. 2013).

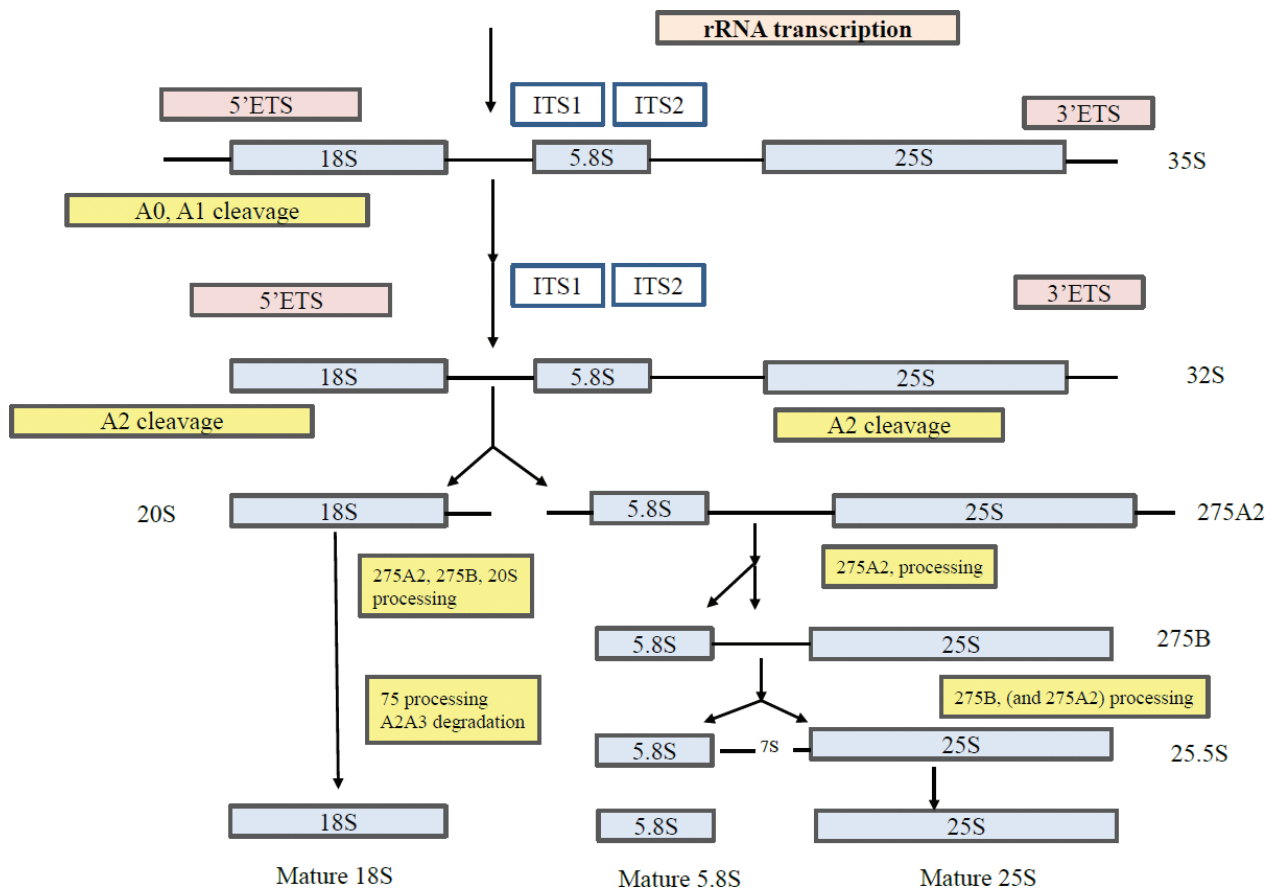
### The assembly of ribosomal subunit 40S

Both processes, pre-rRNA processing and ribosomal protein binding to pre-pre-18S rRNA, occur in the nucleolus. In yeast, the rRNA processing occurs at four step of rRNA cleavage to produce maturation of 18S rRNA – two each on the 5' and 3' ends, which first cleave nearby and then at the mature site (Fernández-Pevida et al. 2015). The independent study shows a broad class of SSU assembly intermediates in wild type cells. The two early sediments at ~90S contain 23S or 35S pre-rRNAs (Udem and Warner 1972; Liang and Fournier 2006; García-Gómez et al. 2011; Delprato et al. 2014; Sardana et al. 2014). Also it is another later intermediate, which forms in the nucleolus, but is located in the cytoplasm at a steady state. This late sediment at 43S contains 20S pre-rRNA. Finally, the fourth sediment contains 23S rRNA sediment at ~60S (Delprato et al. 2014). This fourth sediment may be related to fifth one observed in the cells in which helicase *Dhr1/Ecm16* is mutated (Sardana et al. 2014). The *Dhr1* factor may be a dead end and observed only in the

absence of *Dhr1*. Because nascent rRNA are cotranscriptionally cleaved at site A2, we do not know whether the presence of 35 pre-rRNA or even 23S pre-rRNA is relevant, as these may be degraded before they are mature (Osheim et al. 2004; Kos and Tollervey 2010; Axt et al. 2014). The ribosomal proteins which will bind to the body of small subunit (SSU) appear to bind during early phase of transcription. Deficiency of these will block assembly and processing at a cleavage site (A0 and A1) at the 5' end of 18S rRNA (Ferreira-Cerca et al. 2005; Ferreira-Cerca et al. 2007). Processing at A2 and D appears to be depending on the prior cleavage at site A1. Processing at site A2 occurs predominantly cotranscriptionally (Osheim et al. 2004; Kos and Tollervey 2010; Axt et al. 2014); the assembly of ribosomal proteins, which are members of this group and make approximately up to 70% of all small subunit ribosomal proteins, must also occur cotranscriptionally. It consists of 21 or 22 small subunit ribosomal proteins, which participate in a significant amount of 20S pre-rRNA, while only *S11* and *S13* participate in a significant amount of 35S rRNA (Ferreira-Cerca et al. 2007). Ribosomal protein *S26* does not participate in 20S pre-rRNA, suggesting that it does not bind until 18S rRNA is matured. A small subset of head ribosomal proteins, such as *S3/uS3*, *S15/uS19*, *S18/uS13*, and *S19/eS19*, is required for export of the nascent subunit (Ferreira-Cerca et al. 2007). Another subset of ribosomal proteins, such as *S10/eS10*, *S20/uS10*, *S26/eS26*, *S29/uS14*, *S31/eS31*, and *Asc1*, may assemble in cytoplasm, and they are required for cytoplasmic processing of 20S pre-rRNA (Ben-Shem et al. 2011) (Fig. 1).

### The assembly of ribosomal subunit 60S

The assembly of ribosomal protein from large subunits is defined by six successive steps of processing of pre-rRNA within pre-60S particles. Only the first step of LSU assembly is cotranscriptional. Production of 60S ribosomal subunit is initiated by cleavage of nascent pre-rRNA at the A2 site. This cleavage occurs after the transcription of RNA pol I has proceeded ~1–1.5 kb 3' along that site (Osheim et al. 2004; Kos and Tollervey 2010; Axt et al. 2014). After the transcription is completed, the first precursors, which are specific for LSU assembly, are formed; it contains 27SA2 pre-rRNA and most of ribosomal proteins, and approximately one-third of the 75 assembly factors, which are important for assembly of LSU (Dez et al. 2004). Many researchers have studied the individual role of ribosomal proteins during LSU biogenesis (de la Cruz et al. 2015). More recently, the roles of most 60S ribosomal proteins have been systematically examined, to measure changes in ribosomal proteins and in purified preribosomal particles (de la Cruz et al. 2015). Depletion of any of 12 ribosomal proteins from 60S large subunits, such as *L3/uL3*, *L4/uL4*, *L6/eL6*, *L7/uL30*, *L8/uL2*, *L13/eL13*, *L16/uL13*, *L18/eL18*, *L20/eL20*, *L32/eL32*, *L33/eL30*, and *L36/eL36*, damage the early step of 27SA2 pre-rRNA processing; depletion of 11 ribosomal proteins



**Figure 1.** Inhibition of rRNA processing at different steps. The rRNA processing scheme from 35S pre-rRNA to the mature rRNA (18S, 5.8S, and 25S) is shown here; sequences are indicated by red color, external transcribed spacers (5'-ETS and 3'-ETS) and internal transcribed spacer (ITS1, and ITS2) are represented by white color. Relative cleavage site positions are indicated, and sites are specified with the pre-rRNA.

from 60S large subunits, such as L9/uL6, L17/uL22, L19/eL19, L23/uL14, L25/uL23, L26/uL24, L27/eL27, L31/eL31, L34/eL34, L35/uL29, L37/eL37, is shown to cause accumulation of 27SB pre-rRNA; other 7 ribosomal proteins from large subunits 60S, such as L2/uL2, L5/uL18, L11/uL5, L21/eL21, L28/eL28, L39/eL39, and L34/eL34, play a pivotal role for processing 7S pre-rRNA or 6S pre-rRNA before nuclear export of preribosomes (de la Cruz et al. 2015).

The ribosomal proteins which are necessary for the first step of 27SA pre-rRNA are bound to domains I and II of 25S rRNA. The ribosomal proteins which are necessary for middle steps of pre-rRNA processing in neighborhood around the exit tunnel are defined by domain I and II of 25S rRNA and 5.8S rRNA. Ribosomal proteins that are involved in the processing of 7S pre-rRNA are located on the intersubunit surface (Chen and Williamson 2013). Many assembly factors, such as Npa1/Urb1, Npa2/Urb2, Dbp6, Dpb7, Dbp9, Rsa3, Nop8 and Rrp5 in cooperation with L3, may participate in maturation of 60S large subunit (Rosado et al. 2007; Lebaron et al. 2013). In a later phase of maturation, other assembly factors involved, such as Nsa2 and Nog2/Nug2. Nog2, are shown to bind helices in domains II, IV and V on the surface of the pre-60S ribosomal particles (Matsuo et al. 2014). In a

later stage of the assembly of large subunits, it has been shown that other factors are also involved, such as Rsa4, Nog2, Rpf2 and Rrs1 (Matsuo et al. 2014) (Fig. 1).

### Ribosomal proteins and disease

Proliferation and growth of cancer cells require huge amount of protein synthesis. This means that cancer cells require higher efficiency from ribosome translation than normal cells. Besides the importance of ribosome in the cell growth and proliferation, some ribosomal proteins may play a pivotal role during the tumorigenesis. Numerous ribosomal proteins have been up-regulated during protein synthesis in various tumors (Chen et al. 2014). Overexpression of RPS3A/eS1 is shown to promote transformation of NIH-3T3 cells and tumor growth in nude mice (Naora et al. 1998). The ribosomal protein from the small subunit RPS13, higher expressed in multi-drug resistance in gastric cancer cells, has shown to promote gastric cancer cell proliferation (Guo et al. 2011). Other ribosomal proteins are shown to play a pivotal role in suppressing tumorigenesis by activation of other tumor suppressors or possible inactivation of oncoproteins (de Las Heras-Rubio et al. 2014). Over the past decades, many other ribosomal proteins, such as RPL5/uL18 (Dai and Lu 2008), RPL6/



eL6 (Bai et al. 2014), RPL11/uL5 (Lohrum et al. 2003), RPL23/uL14 (Dai et al. 2004), RPL26/uL24 (Zhang et al. 2010), RPL37/eL37 (Daftuar et al. 2013), RPS3/uS3 (Yadavilli et al. 2009), RPS14/uS11 (Zhou et al. 2013), RPS26/eS26 (Cui et al. 2014), RPS27A/eS31 (Xiong et al. 2014), have been identified to regulate the MDM2-p53 cascade. The first interaction between ribosomal proteins (RPs) and MDM2 was reported in 1994 by Marechal et al. (1994).

However importance of RPs-MDM2 interaction had remained unreachable for more than 10 years until RPL11/uL5, RPL5/uL18 and RPS23/uS12 were reported to be involved in regulation of the MDM2-p53 feedback loop (Lohrum et al. 2003; Dai et al. 2004; Jin et al. 2004). Most of ribosomal proteins (RPs) are shown to interact with MDM2, some of ribosomal proteins, such as RPS7/eS7 (Zhu et al. 2009), RPS15/uS19 (Daftuar et al. 2013), RPS20/uS10 (Daftuar et al. 2013), RPS25/eS25 (Zhang et al. 2013), and RPL37/eL37 (Daftuar et al. 2013), have been shown to bind to MDM2 homolog and partner of MDM2. RPL26/uL24 (ribosomal protein enhancer) interacts only with MDM2 but also is associated with p53 mRNA and enhances translation (Takagi et al. 2005). The ribosomal protein which interacts with MDM2 is RPS23 and it induces apoptosis (Lee et al. 2010). Akt phosphorylation of RPS3 may play a pivotal oncogenic role, and phospho-RPS3 was shown to translocate into the nucleus and upregulate the pro-survival gene control via association with NF- $\kappa$ B in cancer cells (Wan et al. 2007; Yang et al. 2013). The complex which is built between RPL5/uL18, RPL11/uL5 and 5SrRNA is essential for p53 activation (Horn and Vousden 2008; Donati et al. 2013). Recently many studies have been carried out on both RPL5/uL18 and RPL11/uL5, but not other ribosomal proteins are required for RS-elicited p53 activation (Fumagalli et al. 2012). The oncoprotein factor, such as SRSF1, was shown to be involved in stabilization of p53 as an indispensable component of the RPL5/uL18-MDM2 complex and to trigger oncogene-induced and p53-dependent senescence (Fregoso et al. 2013). Several ribosomal proteins can inactivate oncoproteins, such as c-Myc. RPL11/uL5, which first will be connected to Myc box II (MB II) domain of c-Myc and inhibit transcriptional activity of c-Myc by preventing the recruitment of its transcriptional activity by pre-gene promoters (Dai et al. 2007). RPS14/uS11 and RPL5/uL18 have shown to be involved in suppression of c-Myc activity by direct binding to transcription factors and regulating mRNA (Liao et al. 2013; Zhou et al. 2013). Other ribosomal proteins, such as RPL5/uL18, RPL10/uL16 and RPL22/eL22, in patients with cancers can induce tumor suppressors (De Keersmaecker et al. 2013; Kandoth et al. 2013).

### The potential therapy: inhibition of the Eukaryotic 80S Ribosomes

Many researchers have documented that antibiotics attach to the ribosome in cancer and rare genetic diseases (Wilson 2014; Arenz and Wilson 2016; Lin et al. 2018; Po-

likanov et al. 2018; Vázquez-Laslop and Mankin 2018). These small molecules are synthesized by fungi or bacteria, interacting with a specific site of the ribosome. Many studies have shed light on the implication of protein synthesis inhibition triggered by the binding of antibiotics and how the bacteria can develop the antibiotic resistance. Different antibiotics are documented to connect with Aminoacyl (A), Peptidyl (P), and Exit (E) binding site within 30S and 50S ribosomal subunits (Arenz and Wilson 2016; Lin et al. 2018). Eukaryotic ribosome also is a target of small molecule inhibitors. Several compounds are shown to inhibit protein synthesis at different steps, as is documented by many authors who have published their results (Brönstrup and Sasse 2020; Dmitriev et al. 2020; Burgers and Fürst 2021). These inhibitors, besides being routinely used for research purposes, hold great potential as anti-cancer therapeutics and correctors of genetic disorders (Dmitriev et al. 2020; Gilles et al. 2020). One example is drug omacetaxine mepesuccinate (called homoharringtonine – (HHT)) used for treatment of chronic myeloid leukemia (CML). HHT, marketed as Synribo™, is the first protein synthesis inhibitor approved by the FDA (Food and Drug Administration), which is shown to inhibit tyrosine kinase, which is commonly used as the first line of CML treatment (Kantarjian et al. 2013; Yakhni et al. 2019). Inhibition of A site during elongation is documented by ansiomycin (ANI), agelastatin A (AglA), deoxyvalenol, haemanthamine (HAE), homoharringtonine (HHT), lycorine (LYC), nagilactone C, narciclasine (NAR), T2-toxin, and verrucaric acid (Pellegrino et al. 2021). Inhibitors are shown to have affinity for binding in PTC during elongation of the nascent chain and peptide exit tunnel (PET). Blastidicin S (Bla S) and PF846 are documented to bind within PTC (peptidyl transferase center P-site) (Garreau de Loubresse et al. 2014; Arenz and Wilson 2016; Powers et al. 2021), where the P-site tRNA and nascent chain, respectively, interact with the ribosome. The PF846 binds to the PET and contact residues A1588 and U4525 by establishing two different types of interaction, halogen- $\pi$  and  $\pi$ - $\pi$  stacking, respectively, each mediated by chloride atom (Liaud et al. 2019; Li et al. 2020; Pellegrino et al. 2021). The E site of a large subunit is inhibited also during the translocation process. The drugs which can make inhibition are cycloheximide (CHX) (Garreau de Loubresse et al. 2014), lactimidomycin (LTM) (Schneider-Poetsch et al. 2010), phyllantoxide (PHY) (Garreau de Loubresse et al. 2014), chlorolissoclimide (CL) (Robert et al. 2006), and the synthetic analogue C45. The PHY, in contrast to CHX and LTM, have the possibilities to interact directly with eukaryote ribosomal protein eL42 from large subunits (reviewed in Pellegrino et al. 2021).

The ribosomal small subunit can also be targeted by protein synthesis inhibition. The drugs which can inhibit ribosomal protein synthesis form small subunit are amicoumacin A (AMA) (Pioletti et al. 2001), edeine (EDE) (Pioletti et al. 2001; Dinos et al. 2004), cryptoleurine (CRY), and pactamycin (PAC) (Pellegrino et al. 2021). The decoding center (DC) of the eukaryotic ribosome is a target for many

aminoglycosides, such as paromomycin (PAR), geneticin (G418), gentamicin (GENT) and TC007. PAR has the ability to bind with minor groove of h44 and to promote “flip-out” of the two conserved adenines towards the mRNA channel; GENT also binds to h44, but docks in a different way compared with PAR (Garreau et al. 2014). The aminoglycoside TC007 is shown to interact directly with both subunits LSU and SSU, establishing hydrogen bonds with rRNA residues of the 25S and 18S at a specific intersubunit bridge (B3) (Pellegrino et al. 2021). Hygromycin B (HygB) is another aminoglycoside which is used in the scope of research and is shown to have the ability to bind within a decoding center (DC). The antibiotics such as tetracycline, pactamycin and hygromycin B bind to discrete sites on the 30S subunit in a manner consistent with much but not all biochemical data. These antibiotics act at different sites and in different way, thus they illustrate the great diversity of antibiotic binding sites (Brodersen et al. 2000).

## Conclusion

For many years, the biogenesis of eukaryotic ribosome was studied exclusively in the yeast model system, because it was an easy genetic manipulation and there were possibilities to isolate large amounts of pre-ribosomal complexes for compositional and structural analyses. Major challenges for future will be to determine which factors are important and play a pivotal role during ribosome biogenesis, and to dissect the individual roles of such proteins during subunit assembly.

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The ribosome biogenesis during embryogenesis can cause severe developmental defects, resulting in several human genetic diseases, and whereas restricted ribosome synthesis in cancer cells has profound clinical applications. First of all, the number of ribosomal proteins can enhance the activity of tumor suppressor; for example, p53 activity is highly boosted by ribosome proteins, such as RPL5, RPL11 and others, and whereas dramatically impairs ribosomal proteins-induced p53-dependent cell cycle arrest and apoptosis in different tumor cells. The rapid and active growth and proliferation of tumor cells need more ribosome compared with normal cells. The anti-ribosomal drugs might be less toxic to normal and differentiated cells; and many small molecules have been identified, such as CX-3543, which has the abilities to bind with G-quadruplex structures; CX-5461 is a specific inhibitor of Pol I, and moreover, administration of CX-5461 selectively kills Eμ-Myc lymphoma cells. Therefore, more anti-cancer drugs and gene therapy for genetic diseases will be developed against ribosomal biogenesis in the coming years.

## Conflict of interests

The authors declare no conflict of interests.

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