Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Genetics & Development

New tricks for an old dog: ribosome biogenesis contributes to stem cell homeostasis

Alessandro Brombin[1,2], Jean-Stéphane Joly[1,2] and Françoise Jamen[1,2]

Although considered a 'house-keeping' function, ribosome biogenesis is regulated differently between cells and can be modulated in a cell-type-specific manner. These differences are required to generate specialized ribosomes that contribute to the translational control of gene expression by selecting mRNA subsets to be translated. Thus, differences in ribosome biogenesis between stem and differentiated cells indirectly contribute to determine cell identity.The concept of the existence of stem cell-specific mechanisms of ribosome biogenesis has progressed from an attractive theory to a useful working model with important implications for basic and medical research.

Addresses
[1] CASBAH Group, University Paris-Saclay, University Paris-Sud, UMR CNRS 9197, Neuroscience Paris-Saclay Institute (NeuroPSI), Bât. 32/33, 1 Avenue de la Terrasse, F-91190 Gif-sur-Yvette, France
[2] INRA, USC 1126, F-91190 Gif-sur-Yvette, France

Corresponding author: Jamen, Françoise (jamen@inaf.cnrs-gif.fr)

Current Opinion in Genetics & Development 2015, **34**:61–70

This review comes from a themed issue on **Cell reprogramming, regeneration and repair**

Edited by **Amander T Clark** and **Thomas P Zwaka**

For a complete overview see the Issue and the Editorial

Available online 3rd September 2015

http://dx.doi.org/10.1016/j.gde.2015.07.006

Introduction

Since the publication of the ribosome filter hypothesis [1], ribosomes are considered as important actors in the translational control of gene expression. Surprisingly, in this context, little attention has been given to the way ribosomes are built. Ribosome biogenesis has always been considered a highly conserved process; therefore, results obtained in yeast were thought to reflect the situation in metazoans (see Box 1 for a brief overview of the process). However, the repertoire of ribosome biogenesis factors (RBFs) varies considerably among eukaryotes [2]. In particular, the comparison between yeast and human reveals that RBF exclusions and additions characterize the evolution of this ancient pathway [3,4••]. What then is the role of these newly acquired RBFs? Could they play tissue and/or cell-specific roles thereby finely regulating gene expression at the translational level? In particular, do stem cells and differentiated cells use different ribosome biogenesis pathways? Here, we provide an overview of the most recent literature relevant to ribosome biogenesis in different species, and show that the existence of a stem cell-specific process is no longer simply an attractive speculation, but a useful working model.

To be or not to be (conserved)?

Studies performed in yeast are considered the gold-standard to understand ribosome biogenesis in eukaryotes. Nevertheless, there are several differences between yeast ribosomes and their counterparts in metazoans, suggesting that their respective synthesis pathways are different. Indeed, ribosomes in metazoans contain additional ribosomal proteins (RPs) and longer ribosomal RNAs (rRNAs) compared to yeast [5]. The main differences in ribosome sizes between eukaryotes result primarily from species-specific enlargements in the 25–28S rRNA although the loss or gain of individual proteins is also observed [3]. Additional observations are in favor of a diversity of the ribosome biogenesis pathway in eukaryotes. For instance, mammalian nucleoli have three, rather than two, subcompartments [6]. Moreover, the human nucleolar proteome is bigger than the yeast one [3,7–9]. Recently, bioinformatics analyses performed on yeast genome [2] and a large scale RNAi-based screen on cultured HeLa cells [4••] revealed clear variations in the nucleolar proteome among eukaryotes [7] and the identification of species-specific (or group-specific) RBFs. These factors are completely uncharacterized and may play cell-specific roles.

Independent results showed that known RBF-coding transcripts accumulate in neuroepithelial progenitors in zebrafish [10] and/or appear to be essential for neuroblast survival in fly [11]. The transcriptome of naive human pluripotent stem cells is also enriched in RBFs [12•]. These data raise the hypothesis that both species-specific and evolutionarily conserved RBFs could contribute to the determination of cell identity. In particular, ribosome biogenesis-based control mechanisms of gene expression may exist and contribute to the determination of stem and progenitor cell homeostasis.

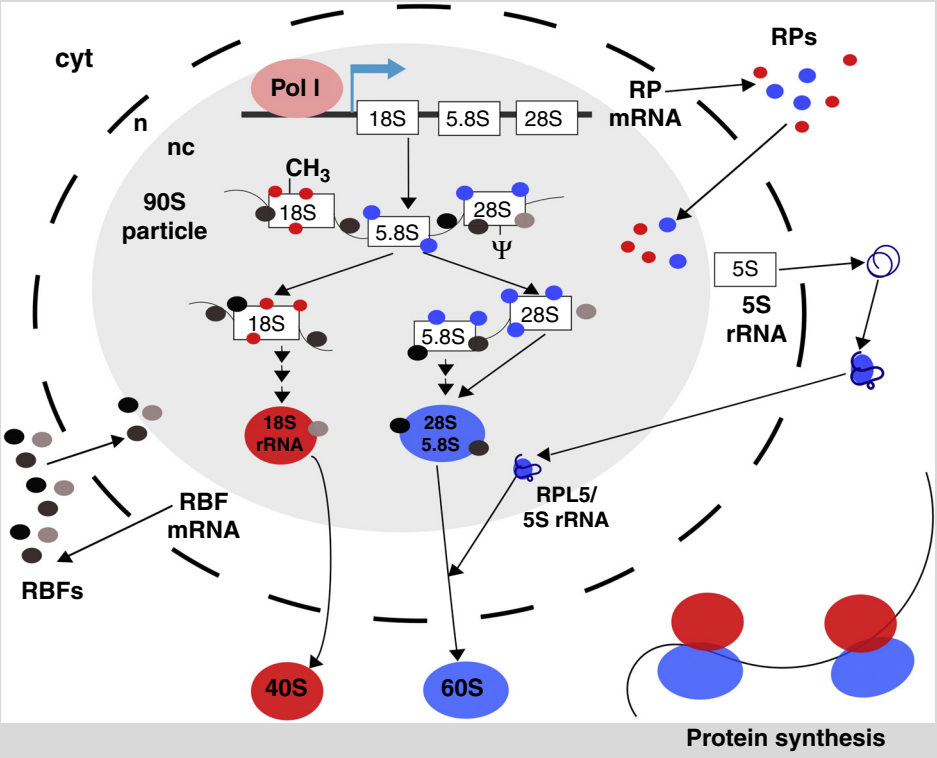
Specificity of ribosome biogenesis in stem cells and progenitors

Recent studies show that different RBFs play specific roles in stem cells and progenitors. Interestingly, this

Box 1 Building the ribosome

Ribosomes are large protein-RNA complexes that translate mRNAs into proteins. They are composed of two subunits. The 60S or large subunit is composed of the 28S (25S in yeast), 5S and 5.8S ribosomal RNAs (rRNAs) and 47 proteins in human; the 40S or small subunit is composed of the 18S rRNA and 33 proteins. Ribosome biogenesis is a highly coordinated, multi-step process that mainly takes place in the nucleolus (nc) but also in the nucleoplasm (n) and cytoplasm (cyt). It requires the activities of the three of RNA polymerases (RNA pol), 75 small nucleolar RNAs (snoRNAs), and more than 250 ribosome biogenesis factors (RBFs). To generate the mature 18S, 28S and 5.8S rRNAs, a precursor 45S rRNA (35S in yeast) is transcribed by RNA pol I as a long polycistronic transcript which is then extensively processed through cleavage and covalent modification events such as 2'-O-methylation (-CH_3) and pseudouridylation (-Ψ). The 5S rRNA is transcribed independently by RNA pol III in the nucleoplasm and undergoes maturation in a separate pathway before being imported to the nucleolus. The ribosomal protein (RP) genes are transcribed by RNA pol II in the nucleoplasm. RBFs include helicases, exo- and endonucleases, methyltransferases and isomerases which modify the nascent rRNA. Other RBFs are required for the nuclear import of RPs and RBFs, maturation and export of ribosomal particles to the cytoplasm and assembly and maturation of the ribosomal subunit particles.

RBFs associate with pre-rRNA to form three types of pre-ribosomal particles: the 90S particle, which is processed into the pre-40S particle and the pre-60S particle. After maturation, the pre-60S and pre-40S ribosomal subunits are exported to the cytoplasm where they undergo final maturation steps to become the mature 60S and 40S subunits, which then associate to form the 80S functional ribosome.



Schematic representation of ribosome biogenesis in human.

applies to many species, which suggests that stem cell-specific regulation exists across the tree of life. Moreover, variations have been evidenced at all steps of the biosynthesis, from rDNA transcription [13,14] to subunit export [15••] (Table 1). Many examples will be presented in the following subsections.

rDNA transcription is differentially regulated in stem cells compared to their differentiated progeny

rDNA transcription is quantitatively regulated in stem cells (Figure 1A) and the rate of rDNA transcription influences cell identity and fate (see the example of FBL in mESC presented at the end of this subsection and in the 'Lost in translation' section). In general, stem cells display higher rates of rDNA transcription than their daughter cells. During differentiation, rRNA synthesis is down-regulated by phenotype-specific transcription factors (like MyoD in the muscle lineage or Runx2 in the osteoblast lineage) (Figure 1A1, right panel) [16]. Although it is generally believed that the down-regulation of rDNA transcription is simply a consequence of the differentiation process, recent findings show that this event actually triggers differentiation. Furthermore, this mechanism may be evolutionarily conserved, as shown