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# Ribosome biogenesis and cancer: basic and translational challenges

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Increasing evidence suggests that alterations in ribosome biogenesis (RiBi) confer competitive advantages to cancer cells. This has led to the discovery of regulatory layers mediated by signaling proteins, oncoproteins, and tumor suppressors whose deregulation leads to increased RiBi rates in cancer cells. In addition to boosting protein synthesis, these alterations probably contribute to shape the protumorigenic proteome of cancer cells. Mutations negatively affecting RiBi are also unexpectedly found in some spontaneous and ribosomopathy-associated tumors. The advantages provided by these genetic lesions to cancer cells remain unsettled as yet. Efforts are being made nowadays to exploit RiBi-associated vulnerabilities and tumor suppressor pathways to design new therapeutic avenues. In this review, we will summarize the main developments and pending challenges in this research area.

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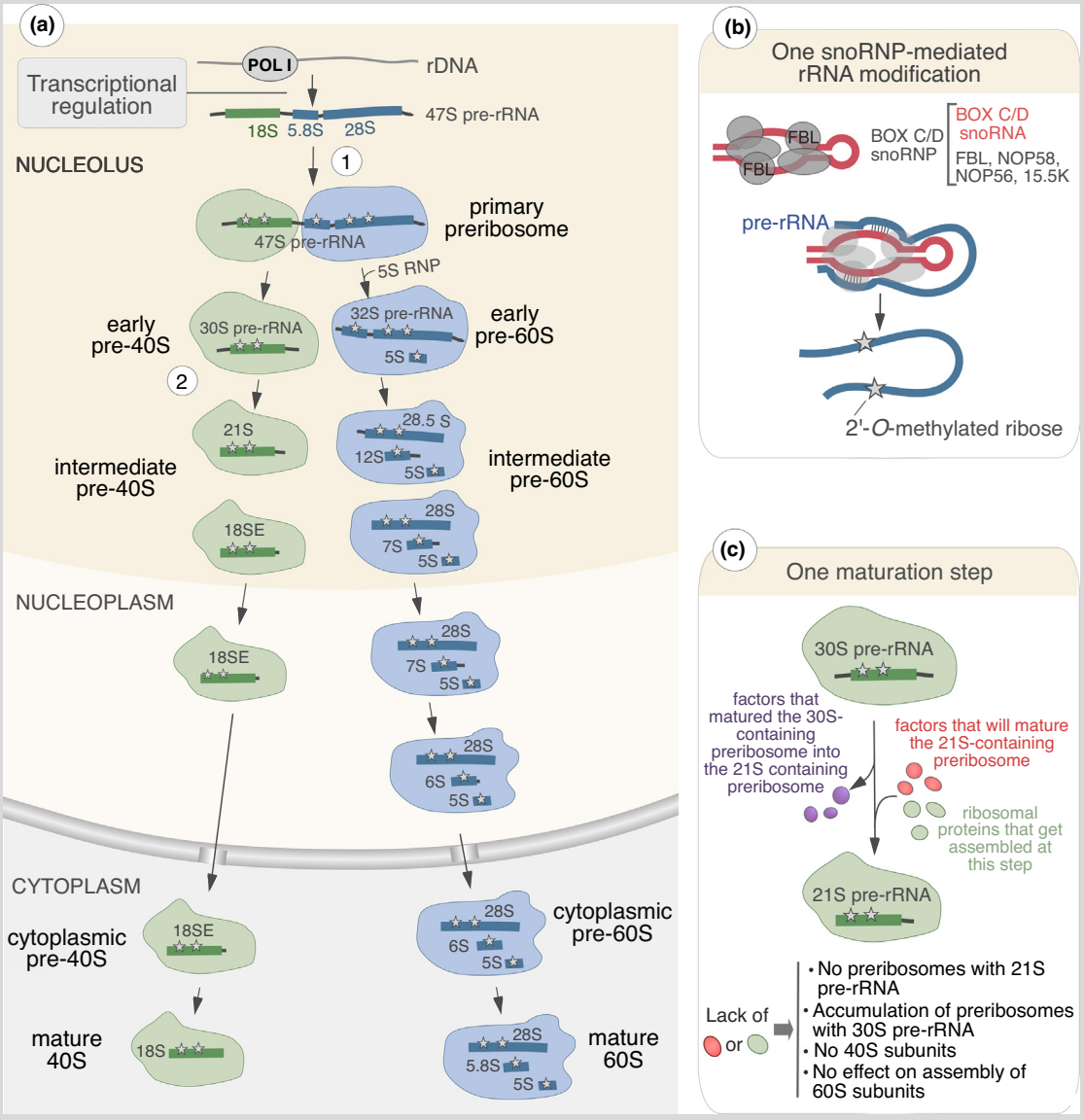
Human ribosomes are composed of a small 40S and a large 60S subunit. The former one contains the 18S rRNA and 33 proteins. The latter one harbors the 28S, 5.8S and 5S rRNAs plus 47 proteins. The biosynthesis of these subunits is a highly orchestrated process that, upon initiation in the nucleolus, continues in the nucleoplasm and the cytoplasm (Box 1). This process requires the action of hundreds of nonribosomal proteins that transiently associate with preribosome intermediates (Box 1) [1–3]. The mechanisms that mediate the assembly and stepwise maturation of these subunits in human cells are not well understood as yet. It is widely assumed that most RiBi steps must be phylogenetically conserved and, therefore, that RiBi must follow a stepwise biosynthetic ladder in human cells similar to that found in the best-characterized model so far: the yeast *Saccharomyces cerevisiae*. However, some features of human ribosomes open the possibility to idiosyncratic species-specific and tissue-specific regulatory mechanisms. Those include the higher complexity of both the inner organization and the proteome of the nucleolus, the larger size of ribosomes, and the signaling challenges imposed by the need of coordinating cell behavior in the context of a multicellular organism. There is also evidence indicating that mammalian cells harbor different subpools of ribosomes with different compositions at the level of core ribosomal proteins [4–6]. There is also little information about the functions of many human-specific RiBi factors and the mechanisms of regulation of this biosynthetic route during physiological conditions and disease states such as, for example, cancer. In this review, we will summarize recent developments regarding the implication of RiBi in this latter disease. To this end, we will focus our attention on new findings regarding the regulation, potential functions, and therapeutic interest of RiBi in tumorigenic processes. Readers can find additional information on the RiBi pathway and particular aspects of its regulation in cancer cells elsewhere [1,2,7,8]. Recent developments about the role of mRNA translation in cancer can be found in accompanying review articles in this issue.

## Alterations of RiBi pathways in cancer

Mounting evidence has underscored the implication of RiBi in cancer cells. However, the molecular mechanisms that contribute to the deregulation of this process only have begun to be understood in recent years. Perhaps not surprisingly, current findings indicate that one of the most common RiBi regulatory points targeted in cancer cells is the RNA polymerase I (POL I) complex itself. This is a logical interference point since this enzyme is involved in the key rate-limiting step of this process, the transcription of the polycystronic 47S pre-rRNA (Box 1a). The stimulation of POL I can be directly elicited by final endpoints of signal transduction pathways frequently deregulated in tumors such as ERK, mTOR, and MYC (Figure 1a,b) [9]. Alternatively, it can be induced by the loss of tumor suppressors and negative cell cycle regulators such as P53, RB, ARF, and PTEN (Figure 1a) [9]. The loss of PTEN also indirectly impacts on POL I activity via the upregulation of the phosphatidylinositol 3-kinase α

**Box 1** The RiBi pathway in human cells. **(a)** Scheme of the pathway required for the biosynthesis of ribosomes. The two independent routes that lead to the formation of the 40S (green) and 60S (blue) ribosomal subunits originate from a common event, the transcription by POL I of a primary precursor (47S pre-rRNA) that contains the 18S, 5.8S and 28S rRNAs embedded in intervening spacers. This transcript is cleaved into two pre-rRNAs that will be subsequently subjected to cleaving and modification steps to generate the mature rRNA components of the two ribosomal subunits. All these steps are carried out in the context of large preribosomal particles each containing different RiBi factors and ribosomal proteins. It is estimated that more than 250 RiBi factors participate in a large number of processes, including the folding and modification of pre-rRNAs, the endonucleolytic and exonucleolytic processing of pre-rRNAs, and the progressive assembly of ribosomal proteins. Ribosomal proteins can be recruited either to the nascent 47S pre-rRNA or during downstream maturation steps (not depicted). The majority of RiBi steps take place in the nucleolus, although some maturation steps occur in both the nucleoplasm (in the case of the 60S pathway) and the cytoplasm (in the case of both the 40S and 60S subunits). The main point of regulation of the pathway (the pre-rRNA transcription by POL I) is indicated. For the sake of simplicity, we have not included all the steps involved in the maturation of the rRNAs. Some of the processes that occur in two of the steps (#1 and #2) are further elaborated in panels (b) and (c), respectively. **(b)** Along the biosynthetic route, the rRNA precursors undergo modifications that include the FBL-mediated ribose methylation and the Dyskerin-dependent pseudouridylation (not shown). These steps require the actions of subcomplexes within the preribosomal particles that are composed of enzymes (gray), ancillary proteins (gray), and snoRNAs of either the box C/D (for methylation, red) or H/ACA (for pseudouridylation, not shown) subclasses. snoRNP, small nucleolar ribonucleoprotein. **(c)** Example of a maturation step showing the dynamic release (RiBi factors from the previous maturation step) and incorporation (RiBi factors, ribosomal proteins) of proteins that take place during that maturation phase. The problems arising from the elimination of a key RiBi factor (red) or ribosomal protein (green) are indicated at the bottom of the box.

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