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Review

p53 and ribosome biogenesis stress: The essentials

Lior Golomb [a], Sinisa Volarevic [b], Moshe Oren [a,*]

[a] Department of Molecular Cell Biology, Weizmann Institute of Science, Rehovot, Israel
[b] Department of Molecular Medicine and Biotechnology, School of Medicine, University of Rijeka, Croatia

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ABSTRACT

Cell proliferation and cell growth are two tightly linked processes, as the proliferation program cannot be executed without proper accumulation of cell mass, otherwise endangering the fate of the two daughter cells. It is therefore not surprising that ribosome biogenesis, a key element in cell growth, is regulated by many cell cycle regulators. This regulation is exerted transcriptionally and post-transcriptionally, in conjunction with numerous intrinsic and extrinsic signals. Those signals eventually converge at the nucleolus, the cellular compartment that is not only responsible for executing the ribosome biogenesis program, but also serves as a regulatory hub, responsible for integrating and transmitting multiple stress signals to the omnipotent cell fate gatekeeper, p53. In this review we discuss when, how and why p53 is activated upon ribosomal biogenesis stress, and how perturbation of this critical regulatory interplay may impact human disease.

1. Introduction

Transformation of normal cells into cancer cells requires dysregulated activity of oncogenes that drive cellular proliferation and survival, alter metabolism and promote invasion into adjacent tissue. Additionally, neoplastic transformation requires inactivation, through mutations, deletions or epigenetic silencing, of tumor suppressor genes that monitor cell homeostasis, block unscheduled proliferation and prevent illegitimate cell survival.

When considering cellular pathways regulated by oncogenes and tumor suppressors, it is not immediately obvious that ribosome biogenesis should be among those pathways. However, a significant body of evidence accumulated over the last 10–15 years suggests that alterations of one or more steps that control ribosome biogenesis are essential for malignant transformation and progression, as many key tumor suppressors and proto-oncogenes have been found to regulate this process (Table 1). Among them, c-MYC and the components of the PI3K-mTORC1 signaling pathway are emerging as key regulators of ribosome biogenesis. So why exactly is a seemingly innocuous process found in the midst of a battleground between powerful positive and negative cellular regulators? The basic explanation is actually rather simple. Cancer is characterized by uncontrolled proliferation of cells, occurring relatively independently of external stimuli [1]. Yet, cell proliferation cannot take place without proper cell growth, namely an increase in cell mass. The increment in cell mass requires extensive protein synthesis, which is dependent on a constant supply of new ribosomes, effectively coupling ribosome biogenesis and protein synthesis to the cell cycle [2]. This is presumably the reason why genes like c-MYC, which control cell cycle progression and DNA synthesis, have evolved to also coordinate ribosome biogenesis and protein biosynthesis [3]. While c-MYC evolved to promote cell proliferation and growth, both under normal conditions and as a driver of malignancy, tumor suppressors like p53 and ARF, one of the two products of the *INK4a* locus, co-evolved as inspectors of cell homeostasis and emerged as gatekeepers of both genomic integrity and ribosome biogenesis.

Reflected by the large number of factors that regulate ribosome biogenesis, the construction of new ribosomes is an elaborate, well-coordinated process, and extremely demanding in terms of energy and resources [4]. It requires the activity of all three RNA polymerases, in order to transcribe both the rRNA and the mRNAs encoding about 80 distinct integral ribosomal proteins (RPs) and other accessory proteins. Ribosome biogenesis also impinges heavily upon the translation apparatus [4] and the nuclear import/export machinery [5,6].

Within the cell, the nucleolus is the main site of ribosome biogenesis (Fig. 1A). It is a sub-nuclear compartment where clusters of

Abbreviations: RPs, ribosomal proteins; NOR, nucleolar organizing regions; ActD, Actinomycin D; MDS, myelodysplastic syndrome; DBA, Diamond Blackfan anemia; SDS, Schwachman–Diamond syndrome; PTM, post translational modifications; 5′TOP, 5′ terminal oligopyrimidine

* Corresponding author. Fax: +972 8 9346004.
E-mail address: moshe.oren@weizmann.ac.il (M. Oren).

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Table 1
A list of reported participants in ribosome biogenesis stress signaling (upper) and key regulators of ribosome biogenesis (lower).

Activators of p53 following ribosome biogenesis stress	
Ribosomal proteins	RPL5 [65], RPL11 [64], RPL23 [66,128], RPS7 [129], RPL26 [91,92], RPS14 [96], RPS3 [130], RPL37 [131], RPS15 [131], RPS20 [131], RPS26 [132], RPS27 [133], RPS27L [133], RPS25 [134]
RNA	5S rRNA [84–86]
Accessory factors	PICT1 [88], nucleostemin [135], SRSF1 [89] NPM [136], NCL [93,137]
Regulators of ribosome biogenesis	
Oncogenic pathways	c-MYC (reviewed in [3]), E2F [138], AKT [139], mTOR (reviewed in [140]), ERK (reviewed in [11])
Tumor suppressors	p53 (reviewed in [10,11]), ARF (reviewed in [115]), PTEN [141], pRB (reviewed in [11])

tandem repeats of rRNA genes are organized into what is known as nucleolar organizing regions (NOR). The rRNA genes are transcribed by RNA polymerase I (PolI) to produce the precursor 47S rRNA with concurrent processing into mature rRNA species [7], followed by assembly of the rRNA together with RPs to form the 40S and 60S ribosomal subunits (Fig. 1A). Notably, different steps of the ribosome biogenesis process are misregulated in a variety of human malignancies, including cancer. A growing number of reports uncover a more complicated picture, where altered activity of the ribosome biogenesis machinery is not merely required to support the rapid proliferation of neoplastic cells, but it might also serve as a driving force in malignancy [8,9]. Thus, the activity of RNA PolI is dysregulated in cancer and other human pathologies [10,11], and enhanced rRNA transcription might attenuate the activity of tumor suppressor genes [8]. In addition to excessive RNA PolI activity, many RPs are overexpressed in human tumors such as colorectal cancer [12,13], esophagus cancer [14] and hepatocellular carcinoma [15]. Cancer cells might benefit from the dysregulation of specific RPs expression, as this might alter quality or quantity of the synthesized tumor promoting proteins [9] or even provide some non-ribosomal advantageous features [16].

Remarkably, alongside its role as the hub of ribosome biogenesis, the nucleolus also evolved into a highly sensitive regulatory hub, which is able to sense various stress signals and initiate a plethora of signaling cascades [17]. Of particular interest is a newly recognized signaling pathway involving ribosomal proteins RPL11 and RPL5 as well as 5S rRNA, which has a unique role in conveying stress messages upon impairment of ribosome biogenesis directly to the Mdm2/p53 module [18]. In this review we describe how the nucleolus and the ribosome biogenesis apparatus serve as unique transmitters of multiple stress signals, which impinge on the tumor suppressor transcription factor p53. We summarize the current knowledge regarding the mechanisms of p53 activation following ribosomal stress, and discuss how malfunctions in the ribosome biogenesis machinery can promote tumorigenesis and how this knowledge might be harnessed towards improving cancer therapy.

2. The nucleolus as a stress sensor

Because the process of ribosome biogenesis is extremely demanding in terms of energy and resources, its fidelity is closely inspected and virtually any type of severe cellular stress will result in an immediate shutdown of rRNA transcription (Fig. 1B) [19]. In response to such stress conditions, including exposure to different genotoxic agents like doxorubicin or inhibition of rRNA transcription using low levels of Actinomycin D (ActD), the nucleolus undergoes distinct structural changes, including condensation and segregation into structures called nucleolar caps, composed of nucleolar proteins and RNA [17,20,21]. Consequently, detection

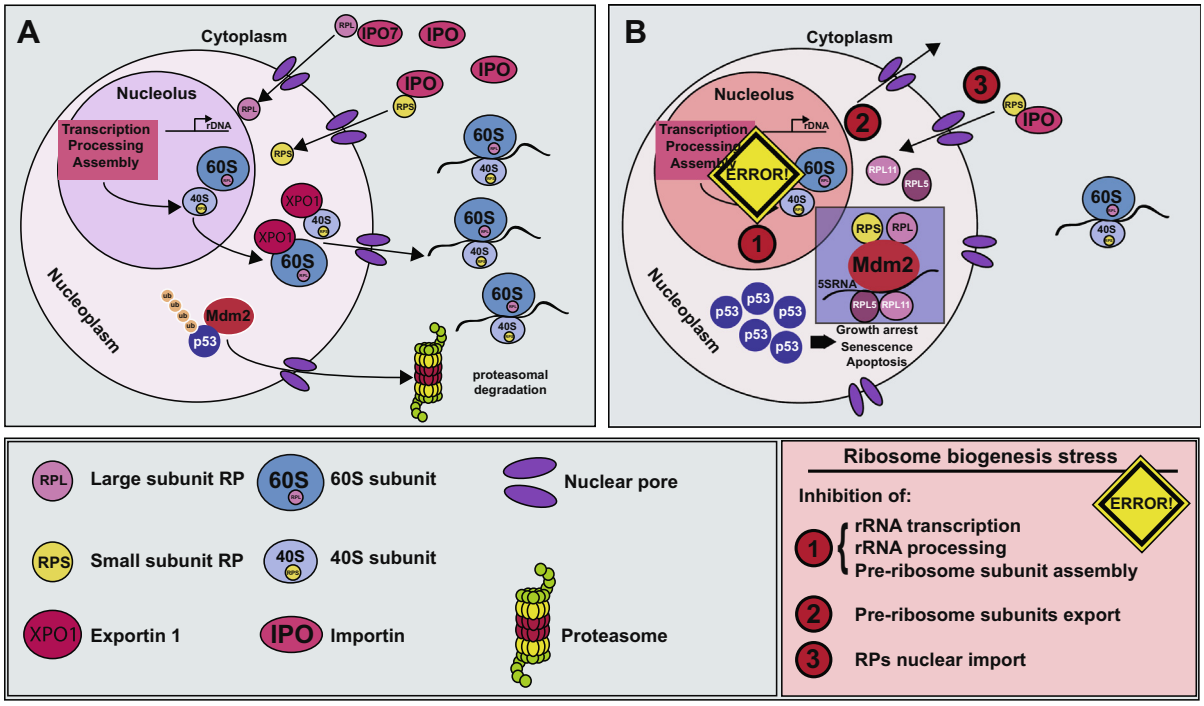

Fig. 1. An overview of ribosome biogenesis, both under normal and stress conditions. (A) Under basal conditions, rRNA is transcribed and processed in the nucleolus. RPs are imported into the nucleolus, where they are assembled together with processed rRNA into the large and small ribosomal subunits (60S and 40S, respectively). Mdm2 binds p53 and polyubiquitylates it, sending it to proteasomal degradation, possibly assisted by nucleolar-mediated export. (B) Inhibition of different steps in ribosome biogenesis can cause unassembled RPs and 5S rRNA to bind Mdm2 and prevent p53 degradation.

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