Seminars in Cancer Biology 37-38 (2016) 36–50

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

The relationship between the nucleolus and cancer: Current evidence and emerging paradigms

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ARTICLE INFO

Article history:
Received 15 October 2015
Received in revised form
15 December 2015
Accepted 19 December 2015
Available online 23 December 2015

Keywords:
Nucleolus
Ribosome biogenesis stress
p53
Genome instability
Cancer

ABSTRACT

The nucleolus is the most prominent nuclear substructure assigned to produce ribosomes; molecular machines that are responsible for carrying out protein synthesis. To meet the increased demand for proteins during cell growth and proliferation the cell must increase protein synthetic capacity by upregulating ribosome biogenesis. While larger nucleolar size and number have been recognized as hallmark features of many tumor types, recent evidence has suggested that, in addition to overproduction of ribosomes, decreased ribosome biogenesis as well as qualitative changes in this process could also contribute to tumor initiation and cancer progression. Furthermore, the nucleolus has become the focus of intense attention for its involvement in processes that are clearly unrelated to ribosome biogenesis such as sensing and responding to endogenous and exogenous stressors, maintenance of genome stability, regulation of cell-cycle progression, cellular senescence, telomere function, chromatin structure, establishment of nuclear architecture, global regulation of gene expression and biogenesis of multiple ribonucleoprotein particles. The fact that dysregulation of many of these fundamental cellular processes may contribute to the malignant phenotype suggests that normal functioning of the nucleolus safeguards against the development of cancer and indicates its potential as a therapeutic approach. Here we review the recent advances made toward understanding these newly-recognized nucleolar functions and their roles in normal and cancer cells, and discuss possible future research directions.

1. Introduction

Ribosomes, the cellular molecular machines responsible for decoding mRNA into protein in eukaryotes, are produced within the most prominent nuclear substructure, the nucleolus [1]. In humans, the nucleolus forms around the nucleolar organizer regions on acrocentric chromosomes 13, 14, 15, 21 and 22 that contain the clusters of ribosomal RNA (rRNA) gene repeats [1]. The rDNA clusters consist of multiple alternating modules of a 47S pre-rRNA coding region and an intergenic spacer (IGS) that harbors the 47S rDNA promoter as well as spacer promotors (SP) that regulate transcription of non-coding RNAs [2]. The nucleolus assembles during late telophase and early G1 phase of the cell cycle, persists throughout interphase and then disassembles at the beginning of mitosis [1]. The mammalian ribosome is a complex structure composed of four rRNAs and ~80 distinct ribosomal proteins (RPs) [3]. The elaborate ribosome structure is largely synthesized and assembled through a number of temporally and spatially organized steps within the nucleolus (Fig. 1). The 47S pre-rRNA is synthesized by RNA polymerase I (RNA Pol I), which requires several transcription factors, including the selectivity factor 1 (SL1), upstream binding factor (UBF), transcription initiation factor 1 (TIF-1A), and transcription termination factor 1 (TTF-1) [4]. It is subjected to highly specific chemical modification (methylation and pseudouridylation) and processed by more than 200 non-ribosomal proteins and small nucleolar RNAs (snoRNAs) into the mature 18S rRNA of the 40S ribosomal subunit and the 5.8S and 28S rRNAs of the 60S ribosomal subunit [5]. In contrast, 5S rRNA is synthesized by RNA polymerase III (RNA Pol III) in the nucleus and assembled into the 60S ribosomal subunit in the nucleolus [5].

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http://dx.doi.org/10.1016/j.semcancer.2015.12.004
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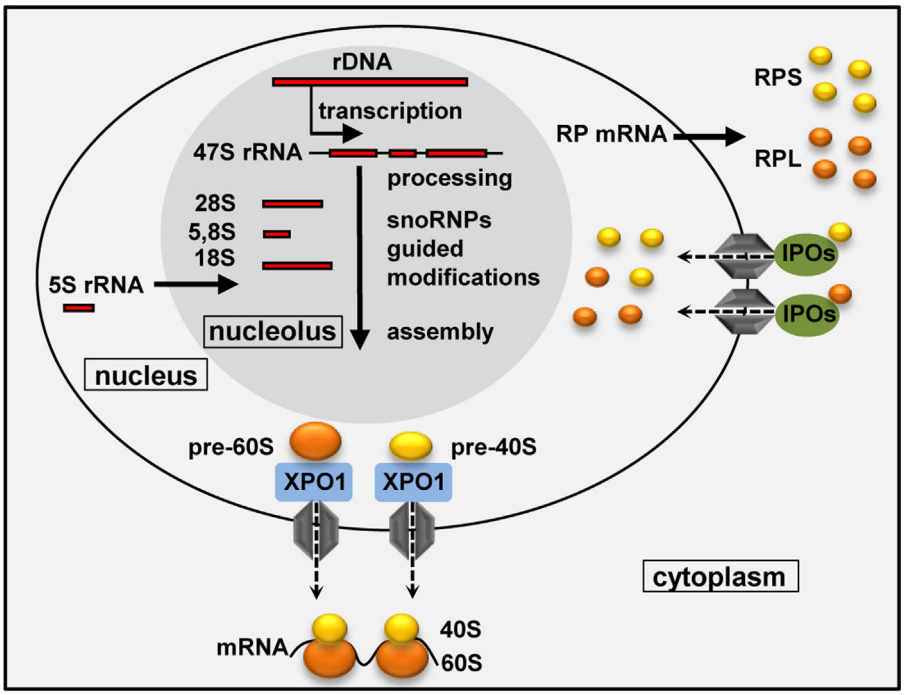

Fig. 1. Eukaryotic ribosome biogenesis. Most steps in ribosome biogenesis are temporally and spatially organized within the nucleolus. The 47S pre-rRNA synthesized by RNA polymerase I is processed and modified by snoRNPs. Following their synthesis in the cytoplasm, most nascent RPs of 40S (RPS) and 60S (RPL) ribosomal subunits are imported into the nucleolus by several importins (IPOs), where they assemble with the rRNA during its transcription and processing. 5S rRNA is synthesized by RNA Pol III in the nucleus and assembled into the pre-60S ribosomal subunit in the nucleolus. The pre-40S and pre-60S ribosomes are exported to the cytoplasm by exportin 1 (XPO1), where final maturation steps take place.

The RP mRNAs are transcribed in the nucleus by RNA polymerase II (RNA Pol II) [6]. Following their synthesis in the cytoplasm, most nascent RPs are imported into the nucleolus where they assemble with the rRNA during its transcription and processing, while a few remaining RPs are incorporated into nascent ribosomes in the nucleus and cytoplasm (Fig. 1) [6]. Different steps of ribosome biogenesis occur at distinct nucleolar subcompartments, namely the fibrillar centers (FCs), dense fibrillar components (DFCs), and granular components (GCs) [7]. The rDNA clusters are located either within or at the periphery of FCs and Pol I-mediated rRNA transcription takes place at FC/DFC interface. Early steps in pre-rRNA processing and ribosome assembly occur in the DFC, while the later steps take place in the GC [1].

The ability of a cell to increase its rate of protein synthesis, a pre-requisite for accurate and timely cell growth and proliferation, is thought to be predominantly mediated at the level of nascent ribosome biogenesis [8]. Given its complexity and enormous energy investment, it comes as no surprise that ribosome biogenesis is tightly coupled with cell growth and proliferation [8]. This process is highly regulated by multiple signaling networks that sense and respond to the availability of nutrients, intracellular ATP levels, growth factors and mitogens or by virtually any environmental and intracellular stressors that perturb cellular homeostasis [7,9]. Failure to properly execute ribosome biogenesis under both favorable growth conditions or cellular stress can create an environment that fosters cancer development as well as a number of other pathological conditions in humans [10]. Increased number and size of nucleoli, which most likely reflect the increased rate of ribosome biogenesis, are frequently observed in malignant tumors such as those of the breast, liver, large-cell lung carcinoma and Hodgkin's disease [11]. Although it can be argued that upregulation of ribosome biogenesis is necessary to provide sufficient translational capacity for rapid and sustained growth and division of malignant cells, recent findings have provided some evidence that it may have a causal role in malignant transformation and cancer progression [11,12]. In marked contrast to that view, small nucleoli, most likely reflecting decreased rates of ribosome biogenesis, are a diagnostic trait of some of the most rapidly proliferating human tumors, including small-cell anaplastic lung cancer and certain types of hematological malignancies [13]. Irregularly shaped nucleoli are also frequently seen in malignant cells [13]. The mechanisms accounting for these differences in nucleolar shape in cancer cells and the specific functions affected are currently unknown. The possibility exists that variations in size and shape of the nucleoli could also be caused by dysregulation of nucleolar functions that may be unrelated to ribosome biogenesis [1]. Recent landmark proteomic studies led to the discovery of over 4500 nucleolus-associated proteins [14]. The fact that 70% of nucleolar proteins have a function unrelated to the production of ribosomes, including, among others, regulation of cell-cycle progression, DNA damage sensing and repair, genomic organization and establishment of nuclear architecture, as well as global gene expression, suggests that nucleolar functions might be significantly broader than previously thought [15]. The protein and RNA content of the nucleolus is constantly changing in response to a wide range of physiological and stress conditions although the significance of these changes remains poorly understood [16,17].

One of the most intriguing observation in this research field is that various cellular stressors, including UV and γ radiation, genotoxic chemotherapeutic agents, hypoxia, nutrient and growth factor deprivation, inhibitors of nucleotide synthesis, oncogenes and loss of tumor suppresors, inhibit or hyperactivate various steps of ribosome biogenesis, a condition known as ribosome biogenesis or nucleolar stress (Fig. 2) [16,18,19]. This triggers a number of ribosome biogenesis stress signaling pathways, either dependent or independent of the p53 tumor suppressor, which orchestrate adaptive biological responses and, under certain circumstances, can even have deleterious effects [10,16,20].