Acta Histochemica xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Acta Histochemica

journal homepage: www.elsevier.de/acthis

Review

Ribosome biogenesis and cancer

Massimo Derenzini*, Lorenzo Montanaro, Davide Trerè

Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna 40138, Italy

ARTICLE INFO

Article history:
Received 12 January 2017
Accepted 27 January 2017
Available online xxx

Keywords:
Ribosome biogenesis
Nucleolus
Cell cycle
Cancer
p53

ABSTRACT

There is growing evidence indicating that the human pathological conditions characterized by an up-regulated ribosome biogenesis are at an increased risk of cancer onset. At the basis of this relationship is the close interconnection between the ribosome biogenesis and cell proliferation. Cell proliferation-stimulating factors also stimulate ribosome production, while the ribosome biogenesis rate controls the cell cycle progression. The major tumour suppressor, the p53 protein, plays an important balancing role between the ribosome biogenesis rate and the cell progression through the cell cycle phases. The perturbation of ribosome biogenesis stabilizes and activates p53, with a consequent cell cycle arrest and/or apoptotic cell death, whereas an up-regulated ribosome production down-regulates p53 expression and activity, thus facilitating neoplastic transformation.

In the present review we describe the interconnection between ribosome biogenesis and cell proliferation, while highlighting the mechanisms by which quantitative changes in ribosome biogenesis may induce cancer.

© 2017 Elsevier GmbH. All rights reserved.

Introduction

The history of the relationship between ribosome biogenesis and cancer begins long before the discovery of either ribosomes or the functions of the nucleolus in ribosome biogenesis. In fact, in 1896 Pianese (Pianese, 1896) observed that the cells of malignant tumours were characterized by particularly larger nucleoli than normal cells. These observations were confirmed early in the 20th century and the macronucleolus was considered “unquestionably diagnostic for malignancy” (MacCarty, 1936). Therefore, for a long period, the nucleolar hypertrophy was considered to be a cytological parameter useful for the diagnosis of malignancy. In the second half of the 20th century, a series of studies showed that nucleolar hypertrophy, which frequently characterizes cancer cells, cannot be considered a reliable parameter of malignancy, as it is also observed in normal proliferating cells, and that cancer cell nucleoli do not, generally speaking, harbour specific changes compared to normal cells. (reviewed in: Busch and Smetana, 1970; Koller, 1963). This led to a period of partial lack of interest in this subject. Interest, however, started to grow again with great intensity with (i) the progressive understanding of the mechanisms regulating ribosome biogenesis, (ii) the identification of the nucleolar components where ribosomal (r) RNA takes place, and (iii) the progressive knowledge of genetic and metabolic alterations in cancer cells. A great contribution to this field was made not only by the introduction of new molecular techniques for the molecular investigation of cell functions, but also by the development of a histochemical technique for the visualization in cyto-histological routine preparations of the nucleolar structures engaged in rRNA transcription, and by the possibility of their easy quantification (Derenzini and Ploton, 1991; Derenzini et al., 1990; Ploton et al., 1986; Trerè, 2000). Evidence was then obtained which indicated that (i) the nucleolar changes detected in cancer cells were exclusively related to the variations in the main activity of the nucleolus, ribosome biogenesis, (ii) the ribosome biogenesis regulated cell cycle progression in proliferating cells, and (iii) factors and oncogene products which control cell cycle progression also regulate ribosome production (Derenzini, 2000; Derenzini et al., 2009; Montanaro et al., 2008). In very recent years the interest in the relationship between ribosome biogenesis and cancer increased further after the finding that the rate of ribosome biogenesis controls the expression level of the tumour suppressor p53 and that an up-regulated ribosome biogenesis is associated with an increased cancer risk (Montanaro et al., 2012). The aim of the present review is: (1) to summarize the data concerning the mechanisms that closely connect ribosome biogenesis and cell proliferation, and (2) to discuss how the quantitative changes in ribosome biogenesis may led to cancer. To make it easier for the reader to understand the topics discussed, first a description is given of the main steps in ribosome biogenesis, together

* Corresponding author at: Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Via Massarenti 9, Bologna 40138, Italy.
E-mail addresses: massimo.derenzini@unibo.it (M. Derenzini), lorenzo.montanaro@unibo.it (L. Montanaro), davide.trere@unibo.it (D. Trerè).

http://dx.doi.org/10.1016/j.acthis.2017.01.009
0065-1281/© 2017 Elsevier GmbH. All rights reserved.

with the principle notions on nucleolar structural–functional relationships.

Ribosome biogenesis

Ribosomes are complex ribonucleoprotein particles with a diameter of 25–30 nm which are located free or membrane-bound in the cytoplasm where they are engaged in protein synthesis. Ribosomes are made up of four types of ribosomal RNA (rRNA) molecules and around eighty different ribosomal proteins. Ribosome biogenesis occurs mainly in the nucleolus, being completed later in the nucleoplasm and cytoplasm. Ribosome biogenesis is the result of a series of coordinated steps (reviewed in Grummt, 2010; Lempiäinen and Shore, 2009; Mayer and Grummt, 2006). The transcription of ribosomal DNA (rDNA) occurs in the nucleolus – where there are around 400 copies of ribosomal genes – and requires the assembly of a multiprotein complex which includes the RNA Polymerase I (Pol I) and a number of basal transcription initiation factors at the rDNA promoter. In mammalian cells, at least three basal factors – the ribosomal DNA transcription factor Rrn3 (Stepanchick et al., 2013) (also referred to as Transcription Initiation Factor I (TIF-I) A (Bodem et al., 2000), the Selectivity factor 1 (SL1), and the Upstream Binding Factor (UBF) – are necessary for ribosome gene transcription (Grummt, 2003). After initiation, the transcript is elongated by Pol I. The transcription ends with a set of specific sequence signals, aided by specific termination factors, such as the DNA-bound transcription terminator factor I (TTF-I) and Pol I transcript release factor (PTRF) (Jansa and Grummt, 1999).

The transcription of ribosomal genes produces the 47S rRNA precursor which is then processed to generate the mature 18S, 5.8S, and 28S rRNA. The fourth type of rRNA – the 5S rRNA – is transcribed in the nucleoplasm by RNA Polymerase III (Pol III), and imported to the nucleolus. These rRNAs are then assembled with ribosomal proteins (RPs) to form the large 60S and the small 40S subunits of mature ribosomes. The large 60S subunit contains one each of the 28S, 5.8S, and 5S RNAs, together with 47 ribosomal proteins, called RPLs, whereas the small 40S subunit contains only the 18S RNA and 32 ribosomal proteins, called RPSs. The RPs whose mRNA is transcribed by RNA Polymerase II (Pol II) are synthesized in the cytoplasm and imported to the nucleolus (Odintsova et al., 2003; Vladimirov et al., 1996). The large and small subunits migrate to the cytoplasm, where they make up the final 80S ribosome particle. In the process of ribosome formation, more than 150 non-ribosomal proteins and around 70 snoRNAs are involved (Fatica and Tollervey, 2002; Fromont-Racine et al., 2003; Kressler et al., 2010; Tschochner and Hurt, 2003). The rate of ribosome production in the cell is strictly dependent on RNA Pol I activity, rRNA transcription rate being the limiting step in ribosome biogenesis (Kopp et al., 2007).

From the morphological standpoint a series of structural–functional investigations made it possible to precisely localize the main steps of ribosome formation in different nucleolar components. When using light microscopy on histological sections from routinely processed tissue samples stained with haematoxylin and eosin (H&E), the nucleolus appeared as a roundish body rather homogeneously stained with eosin due to its high protein content (Fig. 1); the electron microscope revealed a substructural organization characterized by the constant presence of three components. These are: fibrillar centres, which are light electrondense, roundish structures, of variable size; the dense fibrillar component, made of densely packed fibrils located at the border of fibrillar centres; and the granular component made of granules that surround the fibrillar components (Fig. 2A). Ribosomal genes are present in the fibrillar components and the newly synthesized rRNA molecules are located in the dense fibrillar component: there they begin their maturation which continues in the granular component, to form ribosome subunits that will be exported to the cytoplasm. In the fibrillar components of the nucleolus, other than rDNA, all the substances necessary for rRNA transcription process are present (Cisterna and Biggiogera, 2010; Derenzini et al., 1990, 2006; Hernandez-Verdun et al., 2010; Ploton et al., 2004; Raska et al., 2006). Therefore these nucleolar components are the structural functional units of the nucleolus (Sirri et al., 2008). It is worthy of note that these structural–functional units can be easily visualized also by a light microscope. In fact, among the substances which are present in the fibrillar components, there are some proteins–such as the largest RNA polymerase I (RPI) subunit, the upstream binding factor (UBF), nucleolin and nucleophosmin – which are selectively stained by the same silver-staining method used to visualize the nucleolar organizer regions (NORs) on metaphase chromosomes (Roussel and Hernandez-Verdun, 1994). When using this silver staining procedure, only the fibrillar centres plus the associated dense fibrillar component are stained in the nucleolus (Fig. 2B). At the light microscopic level, the structural–functional units of the nucleolus appear as black dots (Fig. 3A), which correspond to the sites where rRNA transcription takes place (Fig. 3B). Therefore, by evaluating these silver-stained structures – simply called AgNORs – at the light microscope level in routinely processed cyto-histological samples, it is possible to obtain information on the rate of the ribosome biogenesis in cells (Derenzini, 2000). As a matter of fact, there is evidence that the amount of the AgNORs is directly related to the rRNA transcription rate (Derenzini et al., 1998, and Fig. 4) and, therefore, to the rate of ribosome biogenesis.

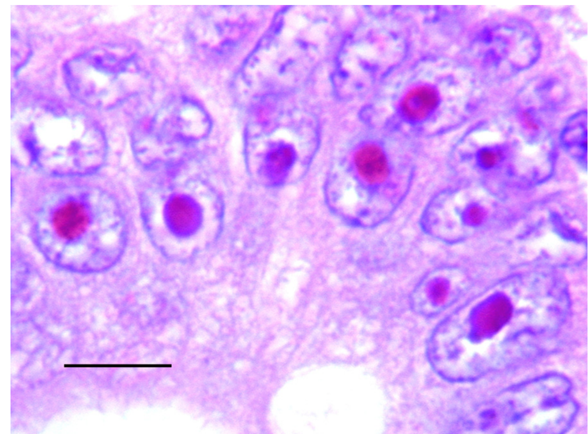

Fig. 1. Routinely processed tissue section from a human colonic carcinoma sample stained with haematoxylin and eosin. Nucleoli are intensely stained in red by eosin as a consequence of their high protein content. Bar = 10 μm.

Ribosome biogenesis and cell cycle progression

When a cell is stimulated to split (cell proliferation), protein synthesis increases greatly so as to duplicate the cell structural and functional components (cell growth) and ensure the generation of normal-sized viable cells (Thomas, 2000). The increased demand for protein synthesis is met by the up-regulation of the ribosome biogenesis rate (Thomas, 2000; Conlon and Raff, 1999). An efficient ribosome biogenesis is necessary for the cell progression through the cell cycle phases (Volarevic et al., 2000), while the achievement of an adequate ribosome complement during the G1 phase makes it possible for the cell to overcome the G1-S phase restriction point (Derenzini et al., 2005), which defines the limit beyond which the cell is committed to split independently of growth (Pardee, 1989; Riddle et al., 1979). Therefore, cell proliferation should be closely coordinated with the biosynthetic

Please cite this article in press as: Derenzini, M., et al., Ribosome biogenesis and cancer. Acta Histochemica (2017), http://dx.doi.org/10.1016/j.acthis.2017.01.009

Download English Version:

https://daneshyari.com/en/article/5504189

Download Persian Version:

https://daneshyari.com/article/5504189

Daneshyari.com