The nucleolus – a gateway to viral infection?

Brief Review

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Summary. A number of viruses and viral proteins interact with a dynamic sub-nuclear structure called the nucleolus. The nucleolus is present during interphase in mammalian cells and is the site of ribosome biogenesis, and has been implicated in controlling regulatory processes such as the cell cycle. Viruses interact with the nucleolus and its antigens; viral proteins co-localise with factors such as nucleolin, B23 and fibrillarin, and can cause their redistribution during infection. Viruses can use these components as part of their replication process, and also use the nucleolus as a site of replication itself. Many of these properties are not restricted to any particular type of virus or replication mechanism, and examples of these processes can be found in DNA, RNA and retroviruses. Evidence suggests that viruses may target the nucleolus and its components to favour viral transcription, translation and perhaps alter the cell cycle in order to promote virus replication. Autoimmunity to nucleolin and fibrillarin have been associated with a number of diseases, and by targeting the nucleolus and displacing nucleolar antigens, virus infection might play a role in the initiation of these conditions.

Introduction

The eukaryotic nucleus contains a number of domains or subcompartments, which include nucleoli, nuclear Cajal bodies, nuclear speckles, transcription and replication foci, and chromosome territories [34]. For many years the exclusive function of the nucleolus was thought to be ribosomal rRNA synthesis and ribosome biogenesis. Recently, however, the nucleolus has been implicated in many aspects of cell biology that include functions such as gene silencing, senescence, and cell cycle regulation [8, 50, 51].

The nucleolus is the site where 5.8S, 18S and 28S rRNAs are transcribed, processed, and assembled into ribosome subunits [52]. The nucleolus is composed...
of (or contains) many different factors including: nucleolin, fibrillarin, spectrin, B23, rRNA, and ribosomal proteins S5 and L9 [63, 65]. Electron microscopy revealed that the nucleolus consists of at least three different regions; fibrillar centres, a dense fibrillar component and a granular component [63]. These regions may have different functions. For example, the perinucleolar compartment has been implicated in RNA metabolism [29].

Nucleolar antigens

Three of the most abundant and well-understood proteins in the nucleolus are nucleolin, fibrillarin and B23. Nucleolin (first called C23), represents approximately 10% of the total nucleolar protein content and is highly phosphorylated, methylated, and also can be ADP-ribosylated [25]. Nucleolin has the potential to bind to multiple RNA targets and this may reflect its variety of functions [25, 26]. One of the main functions of nucleolin is facilitating the first cleavage step of rRNA in the presence of U3 snoRNP. Nucleolin may function as a chaperone for correct folding in pre-rRNA processing [27]. Nucleolin has also been implicated as a repressor of transcription [78]. Whilst mammalian nucleolin has a predicted molecular mass of approximately 77 kDa (depending on the species), the apparent molecular mass is between 100 and 110 kDa, and has been attributed to the amino acid composition of the N-terminal domain, which is highly phosphorylated [25].

Fibrillarin has a molecular mass of approximately 35 kDa and is highly conserved in sequence, structure and function in eukaryotes, and analysis indicated that human fibrillarin has a potential RNA binding domain in its central part [3]. Fibrillarin is directly involved in many post-transcriptional processes including pre-rRNA processing, pre-rRNA methylation, and ribosome assembly [75].

B23 (also called numatrin, nucleophosmin or NO38) is widely distributed amongst different species with approximately the same molecular mass of 35–40 kDa [44, 65]. Two isoforms of the protein are expressed, the major form (B23.1) is predominately located in the nucleolus and the minor form (B23.2) is located in the cytoplasm. Similar to nucleolin and fibrillarin, B23 is likely to have multiple functions and has been implicated in ribosome assembly [17], binding to other nucleolar proteins, nucleocytoplasmic shuttling [37] and possibly regulating transcription of rDNA by mediating structural changes in chromatin [49].

The nucleolus and the cell cycle

The nucleolus and associated proteins are also implicated in (and regulated by) the cell cycle [8]. During interphase in higher eukaryotic cells the number of nucleoli vary depending on the stage of the cell cycle, and the nucleolus disappears at the start of mitosis [2]. During G1 cells can contain more than one nucleolus. This is probably reflected in the fact that these cells are translationally active, and therefore require more ribosomes, whose synthesis may in turn be controlled by the phosphatidylinositol-3-OH kinase (PI(3)K) pathway [74]. As the cells progress through S phase and into G2, where single nucleoli can be present. The nucleolus then disperses during mitosis. At telophase nucleogenesis involves