



Nucleolus Modulates the Shuttle of Telomere Components between Nucleolus and Telomere

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Introduction

Nucleolus was first described about two centuries ago, functioning as the factory of rRNA transcription, processing and assembly of ribosome. While recently studied reported that it can also participate in other bioprocesses such as cell cycle arrest, cellular senescence, protein sub-nuclear distribution and cancer cell proliferation, except its ribosome role. Shelterin as well telomerase is critical for the integration and length maintenance. Here are some studies found that some telomere components like telomere was also accumulated in nucleolus and its retention in nucleolus was regulated by nucleolus protein which is indispensable for the matured of telomerase. Our recent study also demonstrated that TRF2, a member of shelterin, also settled in nucleolus and its telomere protection function was affected by the shuttling between nucleolus and telomere. Here, we review the recent research on the communication between nucleolus and telomere with emphasis on the potential and valuable research direction.

Multiple Function of Nucleolus

A “real nucleus” which is composed with membranes to envelope genome is the major difference between the prokaryote and eukaryote and the nucleolus is the most prominent structure for the eukaryote nucleus. Although the nucleolus has been described for almost two centuries ago, it was first named as “nucleolus” in 1839 by Thiry et al. [1]. During 1960s, benefits from the development of electron microscopy, a tripartite structure of nucleolus was described including the dense fibrillar component (DFC), brillar center (FC) and granular component (GC) [2-4]. The rRNA transcription and processing function of nucleolus was gradually revealed thus it was also known as “the factory of ribosome” for a long period [5]. About half a century later, the new functions of nucleolus addition to the ribosome biosynthesis were found owing to the development of confocal and bioinformatics analysis, leading to the concept of multiple functions of nucleolus [6] which summarized as follows: (i) many proteins unrelated to ribosome assembly, such as ADAR2, Hsp70, RDM1 as well as some viral proteins were detected in the nucleolus, which are closed with signal recognition particle assembly, RNA editing, small RNA mediation, nuclear export, telomerase maturation, cell cycle arrest and stress sensor [7]; and (ii) many nucleolus proteins are also present in the other subcellular organelles or shuttle between the nucleolus and other components in different conditions and/or interact with different subunits for modulating the function of these proteins, for example, nucleolin and CSIG can move out of the nucleolus to bind MDM2 and p53 thus to prevent their degradation [8-10].

The Critical Role Telomere Components on Telomere Protection

The telomeric DNA is composed of double-stranded (ds) short tandem repeats, ranging from protists to higher mammals. The telomeres strand constitutes the 3'-end is rich in guanosine and devoid of cytosine, which are called the G- and C-strands on the basis of

their G/C bias [11]. Due to the end-replication problem, every round of DNA replication results in loss of the terminal sequence and thus progressive shortening of the chromosome end, when it reaches a critical length, telomeres initiate DNA damage response and promote cellular senescence [12]. Additionally, the special naked terminal structure will active the DNA damage signal if there are no telomere guard proteins cover them. While interestingly, there are certain mechanisms that protect and preserve DNA ends. Firstly, the activation of telomerase, a ribonucleoprotein complex comprised telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC) plays an important role for telomere length maintenance [13,14]. Also, Mammalian telomeres contain a specific protein complex, shelterin, that acts as the police to keep the telomeres away from DNA damage responders (Figure 1). Shelterin was composed with six proteins including Telomeric Repeat binding Factor 1 and 2 (TRF1 and TRF2), Protection of Telomeres 1 (POT1), TRF1-Interacting Nuclear protein 2 (TIN2), the human ortholog of the yeast Repressor/Activator Protein 1 (Rap1) and TPP1 [15], among which TRF2 coats the length of all human telomeres and binds the telomere DNA duplex TTAGGG repeats directly and form t-loop-like structures thus hides the overhang of DNA ends [16].

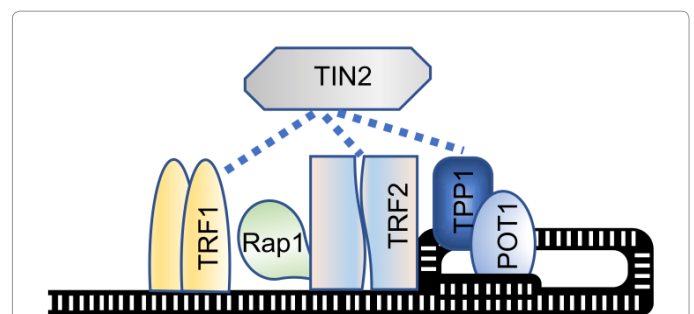


Figure 1: The structure of human telomeres and the potential position of shelterin. Human chromosomes end in an array of TTAGGG repeats that varies in length. The telomere terminus contains a long G-strand overhang that forms the t-loop structure. Telomeric double strands DNA repeats directly interacting with TRF1 and TRF2 and the binding of POT1 to the single-stranded TTAGGG repeats, telomeres contain numerous copies of the complex bound along the repeat array.

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Communications between the Telomere and Nucleolus

The communication between the telomere and nucleolus was firstly reported by Kennedy et al. [17] who found that the redistribution of silencing proteins from telomeres to the nucleolus is associated with extension of life span in *S. cerevisiae*. Later research found that nucleolus was required for the maturation of telomerase and interacted with nucleolus protein nucleolin. The subnuclear shuttling of human telomerase is in a cell cycle depend manner, which could also be induced by transformation and DNA damage [18,19]. Furthermore, other nucleolus proteins such as PinX1, nucleostemin (NS) and GNL3L also interact with telomere proteins and involve in the regulation of telomere length and cell senescence [20,21].

NOLC1 Regulates the Nucleolus Accumulation of TRF2

In our recent study (Figure 2) [22], we found that telomere protein TRF2 localizes in the nucleolus and its nucleolar retention was regulated by nucleolar and coiled-body phosphoprotein 1 (NOLC1), a nucleolus protein that is responsible for nucleolus structure maintenance [23]. Knockdown or overexpression of NOLC1 didn't affect expression of TRF2, but influenced its nucleolar accumulation. Ablating NOLC1 promoted the release of nucleolar TRF2 into nucleoplasm and the number of nucleoplasmic TRF2 foci was increased in hepatoma carcinoma (HCC) HepG2 cells. Conversely, NOLC1 overexpression promoted the accumulation of TRF2 in the nucleolus. In addition, chromatin isolation and ChIP assays demonstrated that the nucleoplasmic level of TRF2 and telomere binding were decreased upon NOLC1 overexpression. Given that NOLC1 modulated TRF2 shuttling between the nucleolus and telomere, we further investigated if this influences the telomere DNA damage response. Indeed, NOLC1 overexpression enhanced the activities of 53BP1 and rH2AX as well as the binding of 53BP1 to telomeres. In addition, the number of 53BP1 foci was decreased upon NOLC1 knockdown in HepG2 cells. Moreover, the percentage of apoptotic cells was higher among NOLC1-overexpressing cells than control cells. Cell cycle progression was arrested after heterogenous expression of NOLC1. Co-expression of TRF2 rescued NOLC1 overexpression-induced cell proliferation inhibition and cell cycle arrest. In summary, our study demonstrated that the nucleolus protein NOLC1 interacted with the telomere-binding protein TRF2 and mediated its nucleolar accumulation. NOLC1 overexpression decreased the binding of TRF2 to telomeres, induced DNA damage response at telomeres and thus promoted HCC cell apoptosis and cell cycle arrest.

In addition, with mass spectrometry (MS) analysis, we found that NOLC1 interacts with other shelterin members except TRF2, so it would be interesting to investigate whether other telomere-related proteins are also regulated by nucleolus proteins. What's more, whether TRF2 or other telomere subunits involve in the nucleolus function is also worth thinking. Actually, it has been reported that AtTRB1, a telomeric DNA-binding protein from Arabidopsis, is concentrated in the nucleolus and shows highly dynamic association with chromatin [24].

Conclusion

In summary, considering the critical role of telomere on cell proliferation, cellular senescence and cancer, as well as the importance of nucleolus on multiple biological processes including cancer and cellular senescence, the communication between the nucleolus and telomere such as how nucleolus regulates the telomere functions and whether telomere components impact the nucleolus function are much worthy for further investigation (Figure 3).

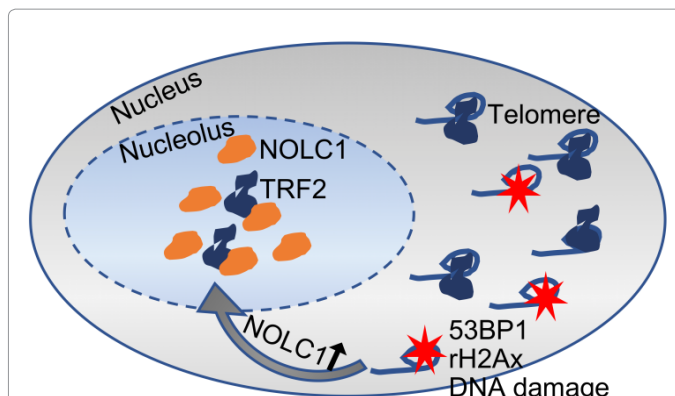


Figure 2: A schematic of how NOLC1 regulates the nucleolar accumulation of TRF2. Under normal conditions, the levels of TRF2 in the nucleolus and at telomeres are strictly balanced. When NOLC1 expression increases, TRF2 accumulates in the nucleolus and disassociates from telomeres, leading to the DNA damage response at telomeres, which promotes HCC cellular apoptosis and cell cycle arrest.

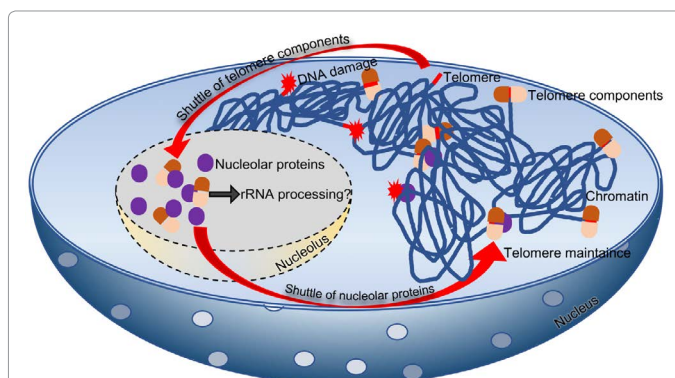


Figure 3: A summary of how nucleolus may communicate with telomere. Emerging evidences support the critical role of nucleolus on telomere components shuttle between nucleolus and telomere and involve in their maturation and/or telomere DNA damages and length maintenance. Besides, nucleolus proteins may also distribute to telomeres and thus participates in telomere protection. On the other hand, whether the telomere proteins that accumulated in the nucleolus are involved in nucleolar functions is worthy for further investigation.

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