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Citation for published version:

Tartakoff, A, DiMario, P, Hurt, E, McStay, B, Panse, VG & Tollervey, D 2022, 'The dual nature of the nucleolus', *Genes and Development*, vol. 36, no. 13-14, pp. 765-769.
<https://doi.org/10.1101/gad.349748.122>

Digital Object Identifier (DOI):

[10.1101/gad.349748.122](https://doi.org/10.1101/gad.349748.122)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Publisher's PDF, also known as Version of record

Published In:

Genes and Development

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PERSPECTIVE

The dual nature of the nucleolus

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The nucleolus is best known for housing the highly ordered assembly line that produces ribosomal subunits. The >100 ribosome assembly factors in the nucleolus are thought to cycle between two states: an operative state (when integrated into subunit assembly intermediates) and a latent state (upon release from intermediates). Although it has become commonplace to refer to the nucleolus as “being a multilayered condensate,” and this may be accurate for latent factors, there is little reason to think that such assertions pertain to the operative state of assembly factors.

The nucleolus is embedded in the nucleoplasm, where it constitutes a compositionally distinct territory. Along with experimental studies of fluorescent proteins that localize to the nucleolus, this partitioning of the nuclear volume has led to repeated assertions that the nucleolus should be considered to be a condensate.

Biomolecular condensates (or membraneless organelles within cells) are composed of multivalent proteins, along with RNA species. These objects tend to be spherical and isotropic and can participate in homotypic fusion. As we discuss below, it remains an open question whether or how condensates participate in ribosome genesis.

In an alternative view, the functional essence of the nucleolus is not that of a condensate but is highly structured. This view dates back to the electron micrographic studies of rDNA repeats (“Miller chromatin spreads”) that showed characteristic “Christmas tree” arrangements of nascent rRNPs that progressively lengthen, form terminal knobs, and undergo cleavage (Miller and Beatty 1969; Osheim et al. 2009). The closely packed “cyclopean” structures of corresponding massive subunit precursors have more recently been imaged by cryo-EM (Baßler and Hurt 2019; Klinge and Woolford 2019; Black and Johnson 2021).

Are these two views compatible?

The generic term “condensate” indicates a separation of territories (often referred to as phases) without implying any underlying mechanism. It is therefore far from specific, especially when used to describe elements within living cells. In contrast, *in vitro* condensates formed from recombinant proteins have been better characterized. In the best-studied examples, their coherence depends on many low-affinity interactions among their multivalent proteins, often dependent on “intrinsically disordered regions” (IDRs). If more than one “type” of *in vitro* condensate coexists, they can exhibit liquid–liquid phase separation (Oldfield and Dunker 2014; Wang et al. 2016; Protter et al. 2018; Mao et al. 2019; Riback et al. 2020; Stenström et al. 2020; Lafontaine et al. 2021).

During early stages of their maturation, nascent small and large ribosomal subunit (SSU and LSU, respectively) precursors are tethered to the rDNA axis that structures their maturation, thereby reducing the dimensionality of assembly. In this process, what role(s) might one or more type of condensates play? Here we discuss the structured versus condensate-based duality as being of central importance for understanding ribosome biogenesis. In addition, we emphasize that experimental probes of the nucleolus must be functional and be expressed at physiological levels if they are to report on the normal biology of subunit maturation.

Known subcompartments of the nucleolus

In many types of higher eukaryotic cells, one can detect three classical subcompartments within the nucleolus. In favorable circumstances, they can be distinguished ultrastructurally and by localizing selected proteins, some of which are known to be ribosome assembly factors (AFs). The compartments are the fibrillar center (FC), the dense fibrillar component (DFC), and the granular component (GC). Analysis of the significance and composition of these compartments is incomplete and is

[*Keywords:* condensates; nucleolus; ribosome genesis]

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Article is online at <http://www.genesdev.org/cgi/doi/10.1101/gad.349748.122>. Freely available online through the *Genes & Development* Open Access option.

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complicated by the realization that the localizations of many AFs are dynamic and can shift according to whether ribosomal subunits are being produced (Phair and Misteli 2000; Chen and Huang 2001; Ide et al. 2020; Lafontaine et al. 2021; Tartakoff et al. 2021). In fact, many AFs that are loaded onto immature subunits in the nucleolus travel with them to the nucleoplasm or the cytoplasm and then recycle. Others reside primarily in the nucleoplasm or cytoplasm (Hernandez-Verdun et al. 2010; Panse and Johnson 2010; Zisser et al. 2018; Baßler and Hurt 2019).

rDNA and rDNA transcription have been localized to the FC (or FC/DFC interface). Nascent rRNP intermediates then extend from the DFC into the GC, where endonucleolytic cleavage along with extensive remodeling are thought to allow immature subunits to be released (Scheer and Hock 1999; Raška et al. 2006; Pederson 2011). The existence of these subcompartments has given rise to the suggestion that each one may be a distinct condensate (Feric et al. 2016; Lafontaine et al. 2021).

The significance of subcompartments has been further investigated in *Saccharomyces cerevisiae*, where an underlying tripartite organization is also detected. The physical properties of yeast (and human) nucleolar AFs are notably diverse (size: 10–280 kDa, predicted disorder: <10%–80%, isoelectric point: pH 4–11). The average titer of each AF (~0.5 mg/mL in the nucleolus) is stoichiometrically comparable with that of nascent rRNA (Tartakoff et al. 2021; Lin et al. 2022).

In yeast, the nucleolus can be seen to have a “coaxial” structure, with the rDNA axis and its most closely associated proteins being surrounded by two layers of AFs and corresponding rRNA segments. The inner layer includes proteins that contribute to both types of subunit. It is conspicuously enriched in AFs that assemble the SSU. The outer layer, in contrast, is dedicated to production of the LSU. When subunit production is halted, many AFs that otherwise would localize to the inner layer relocate to the outer layer/volume. Like the GC, it extends to the surface of the nucleolus (Tartakoff et al. 2021).

As diagrammed in Figure 1, elongation of rRNA is therefore thought to entail the sequential recruitment of specific AFs from this surrounding reservoir of latent AFs, bringing them to the nascent rRNA (Lin et al. 2022). Assuming that these AFs are most stable in the outer layer, this recruitment could build potential energy into the system, thereby driving subsequent vectorial transport in a thermodynamically downhill direction as rRNP intermediates move centrifugally away from the rDNA axis (Tartakoff et al. 2021). The size of the latent pool presumably depends on the rate of subunit assembly. In biophysical parlance, the latent reservoir may be described as an “active emulsion” (Weber et al. 2019).

The clarity of visualization of the coaxial layers in yeast is made possible by (1) *in vivo* “linearization” of rDNA upon cell cycle arrest (in contrast to its normal tortuous path throughout the nucleolus) and (2) the observation that nascent rRNA in yeast is cleaved in the ITS1 region that lies between the segments that are destined for the SSU and LSU (Osheim et al. 2004). This conveniently removes nearly mature SSU precursors once they have been assembled, thereby making it possible to visualize the underlying structure.

The biological importance of condensates

In vitro condensates resemble organelles that lack a surrounding membrane (Matera et al. 2009; Lin et al. 2015; Banani et al. 2017; McSwiggen et al. 2019; Chen and Mayr 2022; Sharp et al. 2022). *In vivo* condensates might enable pathways to function more efficiently for the following reasons: (1) They shield internal components from the surrounding milieu. (2) They promote the thermodynamically downhill vectorial transfer of cargoes to contiguous compartments (e.g., newly assembled subunit precursors, as described above). (3) They concentrate relevant reactants within their interior (e.g., Zhao et al. 2015).

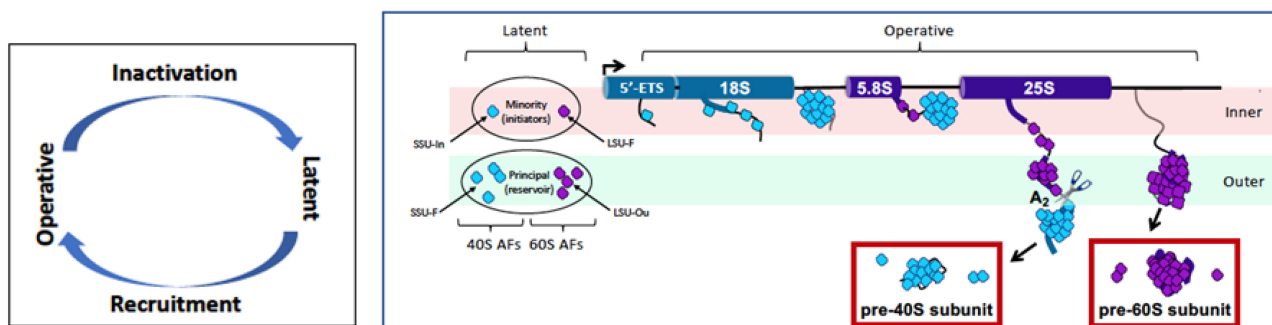


Figure 1. The left panel illustrates the cyclic behavior of ribosome assembly factors, which alternate between having been recruited to immature subunits (operative state) and having been released from them (latent state). The right panel summarizes the processing of nascent rRNAs. The rDNA axis at the top designates the segments that code for distinct domains of rRNA. When latent, almost all assembly factors are broadly distributed, occupying the outer compartment, as indicated at the left. Upon initiation of transcription, these factors are recruited to specific binding sites of nascent rRNPs, progressively forming particulate intermediates that extend from the inner into the outer layer and are ultimately released after endonucleolytic cleavage. The inner layer seems roughly equivalent to the DFC, while the outer layer corresponds to the GC. For a more detailed description, see Tartakoff et al. (2021) and Lin et al. (2022).

In order to probe the interior of the nucleolus, investigators have studied fluorescent proteins that localize to the nucleolus after microinjection into cells and upon expression in living cells (e.g., Brangwynne et al. 2011; Feric et al. 2016; Pillet et al. 2017; Yao et al. 2019; Riback et al. 2020; Lafontaine et al. 2021). Interpretation of these experiments is based on the assumption that the exogenous tracers exhibit behavior that is characteristic of endogenous nucleolar proteins. It has often been taken for granted that they localize to condensates.

Limitations of experiments using fluorescent reporters

Our concerns with such experiments are largely distinct from others who have scrutinized the near universality of condensate biology (Alberti et al. 2019; McSwiggen et al. 2019; Narlikar et al. 2021). There are several issues:

Issue 1: Observations made using fluorescent tracers that are expressed at supraphysiologic levels—or lack functional activity—seem likely to report (at best) on the condition of latent AFs, rather than those that are directly engaged in subunit maturation. In fact, none of the tracers that have been (over)expressed have been proven to retain function, including derivatives of the GC and DFC markers B23/NPM and fibrillarin/FBL/NOP1, respectively. Among the tracers that have been used are engineered reporters that have little resemblance to nucleolar AFs (e.g., Emmott and Hiscox 2009; Scott et al. 2011; Martin et al. 2015; Bracha et al. 2018; Zhu et al. 2019; Riback et al. 2020).

Issue 2: If tracers reach a sufficiently high level within the nucleolus, they could initiate local condensate formation. In this event, they may recapitulate in vitro condensate formation behavior at intracellular sites without being representative of the condition of endogenous proteins engaged in ribosome biogenesis. Considering the elaborate biophysical studies that have depended on the use of fluorescent tracers, this concern is especially important.

Issue 3: The key cell type used for critical early studies (late-stage *Xenopus* oocytes) produces few if any ribosomes (Brown and Littna 1964; Feric et al. 2016). Therefore, the observations made, which led to formulation of the multilayer condensate model, are unlikely to pertain to the operative form of tracers.

Issue 4: There is no reason to expect that studies focused on a single stage of subunit assembly (e.g., the GC markers mentioned above) report on events that occur during earlier or later stages of assembly.

For these several reasons, tracers that concentrate in the nucleolus may or may not report on subunit assembly per se. Given present gene replacement options, greater clarity could surely be achieved in some cases by using tracers that are expressed at normal levels and are known to be functional in genetic complementation assays.

The dual nature of the nucleolus

As a minimal hypothesis, the nucleus can be modeled as including both a nucleosome-filled volume (chromatin)

and an “excluded” nucleolar domain, each of which has self-coherent properties (Hult et al. 2017; Maeshima et al. 2021; Lin et al. 2022). Many nucleolar AFs, like other proteins, include sequences that are predicted to be disordered (Stenström et al. 2020; Lin et al. 2022). However, it is not evident that any resulting interactions are directly relevant to subunit maturation. Moreover, multiple AFs have other types of motifs that can mediate protein–protein binding (WD repeats, HEAT/ARM repeats, complementary charge characteristics, etc.) (Woolford and Baserga 2013; Baßler et al. 2017; Vincent et al. 2018; Lin et al. 2022). Thus, although latent AFs may form condensates, there is little evidence that operative forms should be considered to be part of condensates. Asserting that the nucleolus is a condensate, rather than proving that this is the case, inverts the normal deductive process.

Future studies of the nucleolus

The critical biological roles of the nucleolus and its high complexity have intrigued investigators for decades. Moreover, the nucleolus provides an exaggerated and accessible model of transcription that is relevant to understanding the production and processing of other varieties of RNA. Investigation of the nucleolus has been energized by suggestions that it is fundamentally a multilayered condensate. The facile use of the term “condensate,” unfortunately, has often been used without explicit justification and without attempting to integrate much of the biochemical and cell-biological knowledge that is available. A central unresolved question is whether the many proteins that concentrate in the nucleolus owe their absence from the rest of the nucleoplasm primarily to some shared characteristic that gives them mutual coherence or, rather, that chromatin has some property that restricts intermixing.

Competing interest statement

The authors declare no competing interests.

Acknowledgments

Our work is supported by National Institutes of Health grant R01GM089872.

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Genes Dev. 2022, **36**:

Access the most recent version at doi:[10.1101/gad.349748.122](https://doi.org/10.1101/gad.349748.122)

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