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Nuclear bodies: news insights into structure and function

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The cell nucleus contains a number of different dynamic bodies that are variously composed of proteins and generally, but not always, specific RNA molecules. Recent studies have revealed new understanding about nuclear body formation and function in different aspects of nuclear metabolism. Here, we focus on findings describing the role of nuclear bodies in the biogenesis of specific ribonucleoprotein complexes, processing of key mRNAs, and subnuclear sequestration of protein factors. We highlight how nuclear bodies are involved in stress responses, innate immunity and tumorigenesis. We further review organization of nuclear bodies and principles that govern their assembly, highlighting the pivotal role of scaffolding noncoding RNAs, and liquid–liquid phase separation, which are transforming our picture of nuclear body formation.

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Introduction

Nuclear bodies (NBs) are non-membrane bound structures in the nucleoplasm that fulfill the following requirements: (1.) they are microscopically visible (at least during some periods of the cell cycle); (2.) they concentrate specific nuclear factors, namely proteins and RNAs and (3.) they constantly exchange their components with the surrounding nucleoplasm. The last condition discriminates NBs from protein aggregates that form in the nucleus during certain pathologies, for example, amyloid plagues [1]. NBs appear in a variety of forms ranging from round balls to irregular shape structures. Some of them have uniform inner structure while others (*e.g.*, nucleoli, Cajal bodies or paraspeckles) show further subcompartmentalization. NB formation is generally dynamic, especially in response to a variety of stress conditions [2]. There are numerous bodies present in the nucleus of most cells, including, but not limited to, the nucleolus, Cajal body, PML body, nuclear speckles, paraspeckles, Sam68 body and PcG body (Figure 1). The nucleus may contain additional as yet uncharacterized structures containing specific sets of proteins [3]. Here, we will focus on a few NBs and discuss the latest achievements characterizing their function and structure.

Functions of nuclear bodies

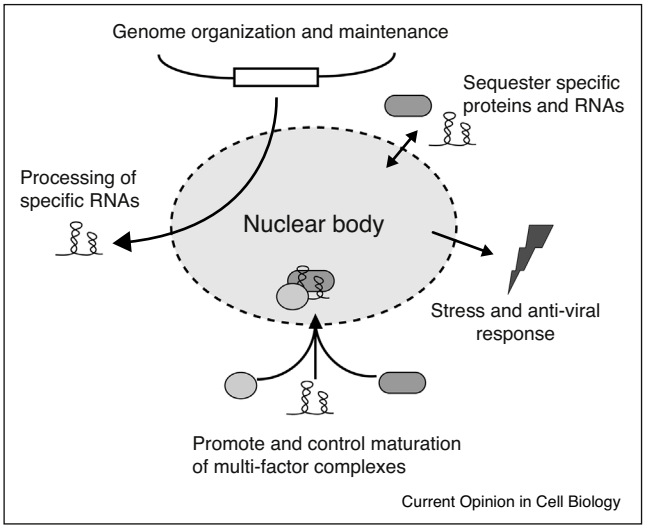
The molecular function of many proteins found in NBs has been described, but whether concentration of these proteins in specific compartments provides cells with an advantage has been a matter of debate for many decades. However, several recent findings support the model that NBs have active roles in nuclear metabolism.

Cajal bodies—master organisers of snRNA biogenesis

Cajal bodies accumulate numerous short non-coding RNAs including spliceosomal snRNAs and snoRNA, that function during rRNA biogenesis. Several studies suggested that Cajal bodies are involved in processing and modifications of snRNAs and assembly of functional snRNPs. Depletion of the major Cajal body protein, coilin, in animal models showed the importance of coilin and Cajal bodies for fecundity and embryogenesis [4,5]. The lethal phenotype in zebrafish is rescued by mature small nuclear ribonucleoproteins (snRNPs) [5], which further supports the model that Cajal bodies promote snRNP assembly [6,7]. Here, we focus on recent work that proposed additional roles of Cajal bodies in short non-coding RNA metabolism.

Cajal bodies associate with snRNA genes (reviewed in Ref. [8]), dependent on active snRNA transcription [9–11]. However, the molecular mechanisms for this association were unclear. New evidence suggests that coilin binds snRNAs *in vivo* [12••], in agreement with studies showing coilin–RNA interactions *in vitro* [13–15]. The emerging model is that coilin binds nascent snRNAs, which leads to snRNA gene association with Cajal bodies (Figure 2a) [12••,16•]. Whether snRNA gene clustering around the Cajal body provides cells with any advantage is unknown, but we speculate that Cajal bodies could stimulate or coordinate transcription of various spliceosomal snRNAs. Indeed, disruption of Cajal bodies by

Figure 1



The scheme summarizes different functions of nuclear bodies discussed in the text.

WRAP53 or USPL1 knockdowns reduces expression of several snRNAs [16•,17].

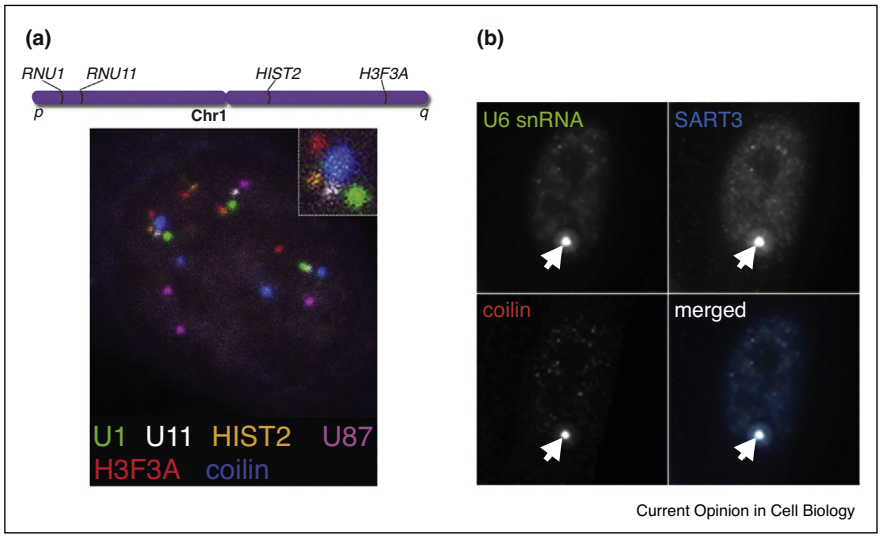
Inhibition of di- and tri-snRNP formation leads to the accumulation of specific snRNP assembly intermediates in Cajal bodies [6,7,18,19•,20]. In addition, inhibition of the final steps of snRNP assembly triggers formation of Cajal bodies in cells that normally lack these NBs and these newly formed Cajal bodies accumulate incomplete snRNPs (Figure 2b) [19•]. These data corroborate earlier findings that Cajal body levels correlate with expression of snRNPs [21]. Thus, the Cajal body emerges as the structure that coordinates, promotes and surveys nuclear phases of spliceosomal snRNP biogenesis.

In addition to spliceosomal snRNAs, hundreds of short non-coding RNAs accumulate in Cajal bodies, but the role of the Cajal body in their metabolism is less clear. The nucleolar U3 snoRNA has been shown to pass through Cajal bodies on its way to the nucleolus [22]. The transient Cajal body localization was shown for several additional snoRNAs and coilin was identified as the Cajal body factor that interacts with snoRNAs [12••]. These data indicate that Cajal bodies are involved in snoRNP biogenesis but it is currently unclear which steps of snoRNA maturation take place in Cajal bodies. TERT RNA has also been found in Cajal bodies that associate transiently with telomeres [23–25]. However, the functional relevance of this association is not known as later studies did not confirm any essential role of Cajal bodies for telomerase RNP formation and telomere maintenance [26,27,28•].

Gems—hubs for factors involved in neurodegeneration

Nuclear gems are enigmatic structures of unknown function. Until recently, the only components localized in gems were members of the SMN complex—the SMN protein and Gemins. In the cytoplasm, the SMN complex is essential for snRNP biogenesis but its role in the nucleus is unclear [29]. Loss of SMN protein results in degeneration of motor neurons and spinal muscular

Figure 2



Function of nuclear bodies. The left micrograph shows organization of snRNA and histone genes found at chromosome 1 around the Cajal body in a HeLa cell nucleus ([16•], courtesy of Mirek Dundr). The right panel shows the Cajal body induced in a primary fibroblast by the knockdown of Prpf6. Prpf6 is essential for U4/U6•U5 tri-snRNP formation and its downregulation blocks tri-snRNP assembly. The U6 snRNA and U6 binding protein SART3 accumulates in the Cajal body after Prpf6 depletion (adapted from Ref. [19•]).