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Review

Finding new roles of classic biomolecular condensates in the nucleus: Lessons from fission yeast

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A B S T R A C T

Decades have passed since the initial discovery of membrane-less nuclear compartments, commonly called nuclear bodies or nuclear condensates. These compartments have drawn attention to their unique characteristics and functions, especially after introducing "liquid-liquid phase separation" to this research field. While the majority of the studies on nuclear condensates have been conducted in multicellular organisms, recent genetic, biochemical, and cell biological analyses using the fission yeast *Schizosaccharomyces pombe* have yielded valuable insights into biomolecular condensates. This review article focuses on two 'classic' nuclear condensates and discusses how research using fission yeast has unveiled previously unknown functions of these known nuclear bodies.

1. Introduction

A great number of cellular biomolecules, such as DNA, RNA, and proteins, are essential for cellular functions. As previously illustrated, these biomolecules are densely packed within a limited cellular space (Goodsell, 1991). Surprisingly, numerous distinct biological reactions, such as metabolic and signaling pathways, are under the tight control of space and time despite the crowded conditions within cells (Ball et al., 2024; Srere, 1987). To achieve this tight control, eukaryotic cells have membrane-bound and non-membrane-bound compartments known as organelles and biomolecular condensates, respectively (Banani et al., 2017; Wheeler & Hyman, 2018). Recent advances in biomolecular condensates have revealed that non-membrane-bound cellular compartments are assembled by liquid-liquid phase separation (Banani et al., 2017; Wheeler & Hyman, 2018) and that the membrane-less compartments serve multiple functions (Banani et al., 2017). For example, they can regulate the kinetics and specificity of biochemical reactions, sequester target proteins to modulate their activities, and act as reservoirs to modulate the cellular concentration of specific molecules (Banani et al., 2017). Since the formation of biomolecular condensates is dynamic and often linked to various factors (e.g., pH, osmolarity, temperature, salt/protein concentration, and posttranslational modifications of proteins that assemble the condensates), the biomolecular condensates can work as 'biosensors' to cellular stress and environmental/developmental cues (Uversky, 2017). Moreover, biomolecular condensates are related to human diseases and aging (Alberti & Hyman, 2021; Morimoto & Boerkoel, 2013). Therefore, membrane-less compartments are critical for normal cellular functions.

Many biomolecular condensates have been documented and are present in the nucleus and cytoplasm (Banani et al., 2017; Spector, 2006). The nucleolus is the best-studied biomolecular condensate in the nucleus (Morimoto & Boerkoel, 2013). The nucleolus is involved not only in ribosome biogenesis but also in sequestering proteins, such as the ubiquitin ligase MDM2 and the transcription repressor DAXX, to prevent them from conducting their functions in the nucleus (Morimoto & Boerkoel, 2013). Another well-known nuclear condensate is paraspeckles (Fox et al., 2018). Paraspeckles are present as 10 to 20 foci in the interchromatin nucleoplasmic space of different human cell types but not in embryonic stem cells (Fox et al., 2002, 2018). The major function of paraspeckles is to control gene expression in distinct ways, such as specific RNA retention and miRNA processing (Fox et al., 2018). In addition, paraspeckles are involved in female reproduction, viral infection, and various cancers (Fox et al., 2018). Thus, phase-separated nuclear compartments have specific roles in various cellular functions.

2. Cleavage bodies

Polyadenylation of mRNAs occurs co-transcriptionally, and two protein complexes, the CPSF (cleavage and polyadenylation specificity factor) and the CstF (cleavage stimulating factor), play an essential role in 3′-cleavage and polyadenylation (Wahle & Rüegsegger, 1999). Immunostaining of the CPSF subunit CPSF2 (CPSF100) or the CstF protein CSTF2 (CstF64) showed that the two proteins were concentrated in 1–4 nuclear foci, which are called cleavage bodies (CLBs) (Schul et al., 1996). CLBs colocalize with transcription factors and contain approximately 20% of newly synthesized RNA (Gall, 2000; Schul et al., 1996), suggesting that mRNA polyadenylation may occur in CLBs. However, the function(s) of CLBs had not been intensively studied before.

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2.1. CLBs also contain RNA degradation factors

We previously performed a localization-based screen to identify the proteins that form nuclear foci in the fission yeast *Schizosaccharomyces pombe* (*S. pombe*). In this screen, we identified the Zn-finger protein Red1/ZFC3H1 (Sugiyama & Sugioka-Sugiyama, 2011). In *S. pombe*, many meiotic genes are transcribed to produce meiotic mRNAs even in vegetative cells, but the YTH domain-containing protein Mmi1/YTHDC1, which colocalizes with the CPF (equivalent to CPSF) constituent Rna15/CSTF2, promotes meiotic mRNA degradation by the RNase complex nuclear exosome (Harigaya et al., 2006; Yamanaka et al., 2010). We found that Red1, which colocalizes with Mmi1, the CPF subunit Pcf11/PCF11, and the nuclear exosome-specific subunit Rrp6/EXOSC10, facilitates the degradation of meiotic mRNAs (Sugiyama & Sugioka-Sugiyama, 2011). In addition, the nuclear poly(A)-binding protein Pab2/PABPN1, which colocalizes with Mmi1, Red1, Rrp6, and the canonical poly(A) polymerase Pla1/PAPOL, is required for the meiotic mRNA degradation (St-Andre et al., 2010; Sugiyama & Sugioka-Sugiyama, 2011; Yamanaka et al., 2010). Moreover, Red1 acts as a binding platform for multiple proteins involved in the meiotic mRNA decay (Dobrev et al., 2021; Foucher et al., 2022), resulting in the assembly of the RNA degradation complex called MTREC/NURS (Egan et al., 2014; Lee et al., 2013; Zhou et al., 2015). Intriguingly, PAXT, a protein assembly equivalent to MTREC/NURS, has been identified in humans and is involved in nuclear RNA surveillance (Meola et al., 2016; Ogami et al., 2017). Although it is unknown whether PAXT colocalizes with CPSF, the PAXT component ZFC3H1, orthologous to Red1, coincides with foci containing poly(A)$^+$ RNA (Silla et al., 2018). These findings indicate that MTREC/NURS is functionally and structurally conserved from fission yeast to humans.

2.2. RNA elimination factors in CLBs and heterochromatin assembly

The RNA elimination factors enriched in CLBs (e.g., Mmi1 and Red1) have been described to direct the assembly of facultative, but not constitutive, heterochromatin at meiotic genes (Hiriart et al., 2012; Lee et al., 2013; Sugiyama et al., 2016; Tashiro et al., 2013; Zofall et al., 2012). However, removing the facultative heterochromatin does not induce meiotic gene expression (Cam et al., 2005; Egan et al., 2014; Tashiro et al., 2013; Zofall et al., 2012). In contrast, human Red1 ortholog ZFC3H1 promotes the formation of facultative heterochromatin by the Polycomb repressive complex 2 (PRC2), resulting in repressing the expression of PRC2-targeted genes (Garland et al., 2019). Thus, while the mechanism of facultative heterochromatin formation appears evolutionarily conserved from fission yeast to humans, the biological significance of facultative heterochromatin at meiotic genes in fission yeast still needs to be determined.

2.3. Additional proteins enriched in CLBs

In addition to Red1, we found that another Zn-finger protein, Red5/ZC3H3, is enriched in CLBs (Sugiyama et al., 2013). Red5 is also required for meiotic mRNA decay and turned out to be a constituent of MTREC/NURS (Egan et al., 2014; Sugiyama et al., 2013; Zhou et al., 2015). Red5 interacts with the mRNA export protein Rmn1 (Egan et al., 2014; Zhou et al., 2015). Moreover, the *Drosophila* Red5 ortholog dZC3H3 reportedly regulates mRNA export (Hurt et al., 2009). We also demonstrated that Rae1/RAE1, another RNA export factor, is essential for meiotic mRNA decay (Sugiyama et al., 2013). These findings highlight the intimate link between mRNA 3′-processing, decay, and export.

Our localization screen also identified Rhn1 as a protein enriched in CLBs (Sugiyama et al., 2012). Rhn1 is an ortholog of the RNA polymerase II (Pol II) transcription termination factor Rtt103/RPRD1, which binds to phosphorylated threonine-4 in the Pol II C-terminal domain (Jasnovidova et al., 2017). Rhn1, which interacts with Pcf11/PCF11, suppresses meiotic mRNA expression during vegetative growth but is indispensable for MTREC/NURS-mediated mRNA decay (Sugiyama et al., 2012). Moreover, the *C. elegans* Rhn1 ortholog Cids-2 suppresses the expression of the germline-specific gene *pgl-1* in somatic cells (Sugiyama et al., 2012), indicating that the Rhn1 function is evolutionarily conserved in fission yeast and *C. elegans*. Intriguingly, Rhn1 binds to a specific chromosomal locus and promotes homologous chromosome pairing during meiosis (Ding et al., 2019). To our surprise, Rhn1 is associated with centromeres in both mitosis and meiosis, although its biological significance is unknown (Ding et al., 2019). Thus, these findings strongly suggest that the proteins enriched in CLBs, such as Rhn1, play an essential role in gene expression and chromosome dynamics in fission yeast.

3. Cajal bodies

The Cajal body, one of the nuclear condensates, was identified over 100 years ago and is frequently associated with the nucleolus and CLBs (Gall, 2000). Cajal bodies (CBs) promote the formation of mature ribonucleoproteins (RNPs), such as snRNPs and snoRNPs (Gall, 2000). Previous reports demonstrated that CBs facilitate snRNA transcription by clustering snRNA genes around CBs and that CBs also act as sites where snRNP assembly and snRNA modifications are complete (Patel & Bellini, 2008; Staněk, 2017). Moreover, additional roles of CBs in NMD (nonsense-mediated mRNA decay), transposon suppression, viral infection, and stress response have been described in plants (Love et al., 2017). Besides, human diseases are linked to several genes encoding CB constituents (Morimoto & Boerkoel, 2013). These findings indicate the importance of CBs, but the nature of CBs and their integral component, Coilin, remains elusive (Machyna et al., 2015). For example, fruit flies lacking Coilin do not show any apparent phenotypic change, while the Cajal body is severely disrupted (Liu et al., 2009). In contrast, Coilin is indispensable for zebrafish embryogenesis (Strzelecka et al., 2010). This variability underscores ongoing debates about the critical functions of Coilin and CBs. Further investigation into Coilin functions in lower eukaryotes, such as yeast and worms, would help us better understand Coilin and CBs. However, no Coilin ortholog had been identified in *C. elegans*, budding yeast, or fission yeast until recently.

3.1. Identification of S. pombe coilin ortholog

In the same localization screen using *S. pombe*, we found that Mug174 (Meiosis upregulated gene 174) localizes as nuclear foci (Deng et al., 2024). A standard BLAST search did not identify any conserved domain or homologous proteins in higher eukaryotes. Characterizing Mug174 and *S. pombe* cells lacking Mug174 (*mug174*Δ) demonstrated that (1) Mug174 often colocalizes with the nucleolus and CLBs, (2) Mug174 forms liquid-like droplets *in vitro*, and (3) Mug174 is required for mRNA splicing and producing viable progeny (Deng et al., 2024). These results suggest that Mug174 is similar to Coilin. Further characterization revealed that (4) Mug174 shows weak homology to human Coilin at the N- and C-terminal domains, (5) Mug174 interacts and colocalizes with TGS1 (Trimethylguanosine Synthase 1), (6) Mug174 associates with U snRNAs and facilitates trimethylguanosine capping of U snRNAs, (7) Mug174 colocalizes with U2 snRNA, and (8) human Coilin expressed in fission yeast colocalizes with Mug174 (Deng et al., 2024). Moreover, a recent protein structure prediction by AlphaFold proposed that Mug174 is a structural homolog of Coilin (Monzon et al., 2022). From these findings, we conclude that Mug174 is the fission yeast ortholog of Coilin (Deng et al., 2024).

3.2. Coilin and centromeres

Coilin has been shown to have additional roles. For instance, when a viral protein or CENP-B depletion damages centromeres, Coilin, but not all CB constituents, relocalizes to centromeres in human and mouse cells (Morency et al., 2007), suggesting Coilin's role in establishing functional

centromeres. Coilin localization to centromeres during the M phase is also observed in *Drosophila* (Liu et al., 2009). In addition, Annexin-A2 overexpression reduces the steady-state levels of two centromere proteins, CENP-A and CENP-C, in a Coilin-dependent manner, thereby causing genomic instability (Kazami et al., 2015). Similarly, partial disruption of pericentromeric heterochromatin and aberrant accumulation of the CENP-C ortholog Cnp3 at kinetochores are observed in the absence of Mug174 (Deng et al., 2024). Therefore, we suspect that Coilin is a conserved regulator of centromeres.

3.3. Coilin: a potential regulator of G0/cellular quiescence

G0/cellular quiescence is a resting state in which cells have exited from mitotic cell division but retain the capacity to revert to the cell cycle in response to appropriate stimuli (e.g., growth factors and nutrition) (Marescal & Cheeseman, 2020). Diverse types of cells, including but not limited to adult stem cells, hepatocytes, lymphocytes, and oocytes, can be in the quiescent state (Marescal & Cheeseman, 2020). Therefore, perturbation in cellular quiescence could adversely affect various functions, such as the immune system and reproduction. Besides, cancer stem cells in cellular quiescence are thought to be the root of resistance to therapies, recurrence, and metastasis (Phi et al., 2018). These findings indicate the biological and clinical relevance of cellular quiescence.

Several model systems are utilized to study the mechanisms of cellular quiescence, and *S. pombe* is one of them (Roche et al., 2017). When G0 was induced, we observed significant reductions in cell viability during G0 and mitotic competence (the ability to restart mitotic cell division) in the absence of Mug174 (Deng et al., 2024), indicating the importance of Coilin (or CBs) in G0. Our analyses uncovered the two roles of Mug174 in G0. One is that the Mug174 promotes the expression of the intron-containing genes essential for cellular quiescence via mRNA splicing (Deng et al., 2024). The other one is that Mug174 evicts RNA polymerase I (*PolI*) from rDNA to prevent rRNA transcription (Deng et al., 2024). In *S. pombe,* rRNA levels rapidly decrease upon G0 induction (Marguerat et al., 2012), and *PolI* transcription is reportedly deleterious in G0 cells (Roche et al., 2016). Since Coilin has been shown to interfere with *PolI* transcription in human cells (Gilder et al., 2011), Coilin-mediated *PolI* transcription suppression seems evolutionarily conserved. From these results, we conclude that Mug174 is essential for cellular quiescence. We anticipate that elucidating the connection between Coilin and cellular quiescence will enhance our understanding of Coilin's (or CBs') functions more broadly.

4. Perspective

Our approach to using fission yeast for studying nuclear condensates has revealed previously unrecognized functions of two known nuclear bodies, CBs and CLBs (Fig. 1) (Deng et al., 2024; Sugiyama et al., 2012, 2013; Sugiyama & Sugioka-Sugiyama, 2011; Zhou et al., 2015). In addition, research from our laboratory, along with findings from others, has proved that *S. pombe* is an invaluable model organism for studying the functions of nuclear condensates in higher eukaryotes.

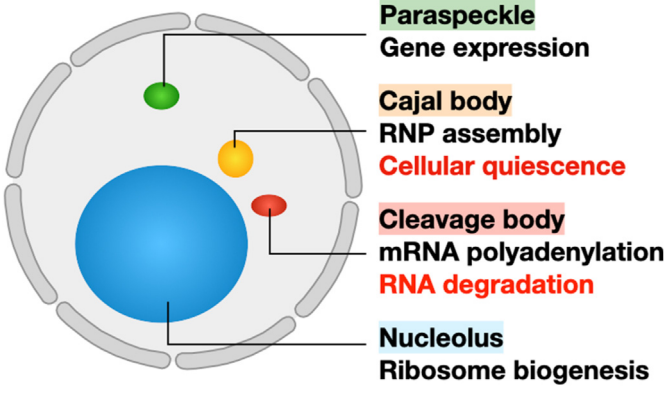

Fig. 1. A schematic representation of the nuclear condensates described in this article. The well-known function (black) and the new role found in *S. pombe* (red) of each condensate are shown below its name.

4.1. Do RNA elimination factors promote the formation of constitutive heterochromatin?

As described above, the RNA elimination factors enriched in CLB (e.g., Mmi1 and Red1) have been described to direct the assembly of facultative heterochromatin at meiotic genes in *S. pombe* (Egan et al., 2014; Hiriart et al., 2012; Lee et al., 2013; Sugiyama et al., 2016; Tashiro et al., 2013; Zofall et al., 2012). Intriguingly, a recent report proposed that MTREC/NURS recruits the H3K9 methyltransferase Clr4/SUV39 to a specific centromeric locus via the long non-coding RNA derived from the locus, thereby nucleating heterochromatin in an RNAi-independent manner (Khanduja et al., 2024). The proposed model is convincing and in agreement with previous models (Buscaino et al., 2013; Reyes-Turcu et al., 2011; Shankaranarayana et al., 2003; Yamada et al., 2005; Yamanaka et al., 2013; Zofall et al., 2012). However, several questions still need to be answered. For example, is Clr4/SUV39 recruited by MTREC/NURS sufficient to initiate heterochromatin assembly? Alternatively, does the artificial tethering of MTREC/NURS, as is the case with RITS (Buhler et al., 2006), recruit Clr4/SUV39 and assemble heterochromatin at an ectopic locus? How does MTREC/NURS engage Clr4/SUV39 specifically to centromeres, though it binds to many euchromatic loci and meiotic RNAs (Hiriart et al., 2012; Lee et al., 2013)? Is MTREC/NURS as critical for the formation of heterochromatin (or for recruiting Clr4/SUV39) as RNAi or the DNA-binding proteins that can attract Clr4/SUV39, such as Atf1 and Taz1 (Jia et al., 2004; Kanoh et al., 2005; Zofall et al., 2016)? Who in MTREC/NURS directly interacts with Clr4/SUV39 (or the Clr4 complex CLRC)? Does the same or similar MTREC/NURS-mediated mechanism work for HOODs, formed in the absence of the nuclear exosome component Rrp6 (Yamanaka et al., 2013)? Answering these questions will provide more information to understand the mechanism of heterochromatin assembly/establishment in fission yeast and, hopefully, in higher eukaryotes.

4.2. Coilin, an evolutionarily conserved protein among eukaryotes

Our work, together with the structural prediction by AlphaFold, concluded that *S. pombe* has the Coilin ortholog (Deng et al., 2024; Monzon et al., 2022), indicating that Coilin is found in most model organisms except for *C. elegans*. Given the essential roles of CBs, worms likely have a nuclear condensate equivalent to CBs. Intriguingly, a standard BLAST search identified Mug174 homologs in multiple *Caenorhabditis* species (e.g., *C. remanei*) except *C. elegans* (our unpublished observation). Therefore, it would be fascinating to explore the functions of the Mug174 homologs in *Caenorhabditis* species and to determine a functional homolog of Coilin in *C. elegens*. The budding yeast *Saccharomyces cerevisiae* (*S. cerevisiae*) lacks any Mug174 homolog (our unpublished observation). However, *S. cerevisiae* has a nuclear structure called the nucleolar body, which is functionally equivalent to CBs (Qiu et al., 2008). Identifying a functional counterpart of Coilin in budding yeast would also be compelling. Further studies using various model organisms would enrich our understanding of Coilin and CBs in higher eukaryotes.

4.3. Coilin functions in higher eukaryotes

We reported that Coilin is essential for adapting to stressful conditions, such as cold and nitrogen starvation in *S. pombe* (Deng et al., 2024). We assume that this Coilin's role in mediating environmental changes is evolutionarily conserved in multicellular organisms. Consistent with this assumption, Coilin in higher eukaryotes is known to alter its localization upon various types of stress (Fefilova et al., 2022). It would be worth

testing whether fruit flies lacking Coilin, which does not show any apparent developmental phenotype (Liu et al., 2009), show a defect under stressful conditions (e.g., DNA damage and dietary restriction) or while aging. Likewise, Mug174 homologs in *Caenorhabditis* species may play a role in dauer formation, which takes place in response to adverse environments (Fielenbach & Antebi, 2008).

S. pombe Coilin is crucial in G0/cellular quiescence (Deng et al., 2024). Considering that G0 is indispensable for cells in a state of reversible proliferative arrest (Marescal & Cheeseman, 2020), our study raised the possibility that CB malfunctions could adversely affect adult stem cells, such as hematopoietic and neural stem cells. Consistent with this idea, immunodeficiency is associated with Hoyeraal-Hreidarsson syndrome caused by mutations in DKC1, a CB component (Knight et al., 1999; Morimoto & Boerkoel, 2013). Further examinations of CBs will likely provide potential clues for developing therapeutic approaches for diseases resulting from their malfunction.

4.4. Biomolecular condensate assembly: to work, or not to work

The diameter of most cellular bodies is in the range of 0.2–1 μm (Banani et al., 2017), making them microscopically visible. However, it is critical to note that visible condensates are not necessarily where your protein of interest works. Biomolecular condensates can serve as storage sites to buffer cellular protein concentration or be assembled to inactivate protein activity, as described previously (Banani et al., 2017; Fox et al., 2018). For example, *S. pombe* Red1, which forms multiple nuclear foci, is highly enriched at the *mei4*$^{+}$ locus by ChIP-chip analyses (Sugiyama & Sugioka-Sugiyama, 2011; Zofall et al., 2012). It was thus plausible that one of the Red1 foci coincided with the *mei4*$^{+}$ locus, but this is not the case (Egan et al., 2014). Therefore, it is essential to investigate the biological significance of forming condensates. Also, your protein of interest may function within small, less visible condensates, suggesting the need for thorough characterization of your protein(s) of interest.

4.5. Does S. pombe have more nuclear condensates?

Our studies identified CBs and CLBs in fission yeast (Deng et al., 2024; Sugiyama & Sugioka-Sugiyama, 2011). However, higher eukaryotes have more nuclear condensates: PML bodies, paraspeckles, and nuclear speckles (Morimoto & Boerkoel, 2013; Spector, 2006). Based on our BLAST search, *S. pombe* appears to lack the marker proteins for these nuclear compartments, but *S. pombe* may have functionally similar condensates in the nucleus — two prior studies identified over 200 or 65 proteins that localize as nuclear foci (Hayashi et al., 2009; Matsuyama et al., 2006). Studying these proteins will yield additional insights into each protein as well as biomolecular condensates in the nucleus.

CRediT authorship contribution statement

Tomoyasu Sugiyama: Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing.

Declaration of competing interest

There is no conflict of interest.

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