

RESEARCH ARTICLE

NUCLEAR DOMINANCE THE ROLE OF CHROMATIN AND RNA IN rRNA SILENCING: BIOLOGY, MECHANISMS AND APPLICATIONS

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ARTICLE INFO

Article History:

Received 15th May, 2026

Received in revised form

29th June, 2026

Accepted 18th July, 2026

Published online 31st August, 2026

Key words:

Nuclear dominance; rRNA gene silencing; Chromatin remodeling; DNA methylation; Histone modification; Ribosomal DNA (rDNA)

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ABSTRACT

Ribosomal RNA (rRNA) gene transcription accounts for most of the RNA in prokaryotic and eukaryotic cells. Nucleolus organizer regions (NORs), which span millions of base pairs, include hundreds to thousands of tandemly repeated head-to-tail rRNA genes in eukaryotes. RNA Polymerase I (Pol I) transcribes these nucleolar rRNA genes, and the expression of these genes is regulated by the physiological requirement for ribosomes. Regulation occurs at several levels, one of which is an epigenetic on/off switch that controls the number of active rRNA genes. Additional mechanisms then fine-tune transcription initiation and elongation rates to dictate the total amount of rRNA produced per gene. In this review, we focus on the DNA and histone modifications that comprise the epigenetic on/off switch. In both plants and animals, this system is important for controlling the dosage of active rRNA genes. The dosage control system is also responsible for the chromatin-mediated silencing of one parental set of rRNA genes in genetic hybrids, a large-scale epigenetic phenomenon known as nucleolar dominance. First described in interspecific plant hybrids and allopolyploids, nucleolar dominance has become a valuable model for understanding RNA-guided chromatin regulation and epigenetic gene silencing. Rather than arising from differences in DNA sequence, nucleolar dominance is established and maintained through coordinated interactions between chromatin remodeling, DNA methylation, histone modifications, and diverse classes of non-coding RNAs. In plants, the RNA-directed DNA methylation (RdDM) pathway, involving RNA Polymerases IV and V, Dicer-like proteins, Argonaute proteins, and 24-nucleotide small interfering RNAs (siRNAs), plays a central role in directing sequence-specific DNA methylation and heterochromatin formation at inactive ribosomal DNA (rDNA) loci. These RNA-mediated pathways function together with ATP-dependent chromatin-remodeling complexes, histone deacetylases, and DNA methyltransferases to establish stable transcriptional repression. In mammals, although classical nucleolar dominance is uncommon, selective silencing of subsets of rRNA genes is regulated through promoter-associated RNAs (pRNAs), long non-coding RNAs, the Nucleolar Remodeling Complex (NoRC), and epigenetic modifications that determine the balance between active and inactive rDNA repeats. Collectively, these mechanisms ensure appropriate ribosome biogenesis, preserve genome integrity, maintain nucleolar organization, and enable cellular adaptation to developmental and environmental cues.

Citation: Mahalakshmi, B.R., Priya, M.D., Divyashree, H.B., K. Ramachandra Kini and Kiran Kumar, H.B. 2026. "Nuclear dominance the role of chromatin and RNA in rRNA silencing: biology, mechanisms and applications", *Asian Journal of Science and Technology*, 17, (08), 14441-14456.

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INTRODUCTION

Ribosomal RNA (rRNA), molecule in cells forms part of the protein-synthesizing organelle known as a ribosome and that is exported to the cytoplasm to help translate the information in messenger RNA (mRNA) into protein (Alberts *et al.*, 2022). The three major types of RNA that occur in cells are rRNA, mRNA, and tRNA (De Robertis *et al.*, 2020). Molecules of rRNA are synthesized in a specialized region of the cell nucleus called the nucleolus, which appears as a dense area within the nucleus and contains the genes that encode rRNA. The encoded rRNAs differ in size, being distinguished

as either large or small. Each ribosome contains at least one large rRNA and at least one small rRNA (Alberts *et al.*, 2022). In the nucleolus, the large and small rRNAs combine with ribosomal proteins to form the large and small subunits of the ribosome (e.g., 50S and 30S, respectively, in bacteria). (These subunits generally are named according to their rate of sedimentation, measured in Svedberg units [S], in a centrifugal field) (De Robertis *et al.*, 2020). The rRNAs form extensive secondary structures and play an active role in recognizing conserved portions of mRNAs and tRNAs (Demongeot *et al.*, 2020). In eukaryotes anywhere from 50 to 5,000 sets of rRNA genes and as many as 10 million ribosomes may be present in a single cell (Kressler *et al.*, 2017). The rRNA genes are organized in tandem repeats. In humans, approximately 300–400 repeats are present in five clusters, located on chromosomes 13 (RNR1), 14 (RNR2), 15

(RNR3), 21 (RNR4) and 22 (RNR5) (McStay, 2016). Diploid humans have 10 clusters of genomic rDNA which in total make up less than 0.5% of the human genome. Mammalian cells have 2 mitochondrial (12S and 16S) rRNA molecules (Laptev *et al.*, 2020) and 4 types of cytoplasmic rRNA (the 28S, 5.8S, 18S, and 5S subunits) (Aubert *et al.*, 2018). The 28S, 5.8S, and 18S rRNAs are encoded by a single transcription unit (45S) separated by 2 internally transcribed spacers (ITS) (Burman *et al.*, 2023). The 45S rDNA is organized into 5 clusters (each has 30–40 repeats) on chromosomes 13, 14, 15, 21, and 22 (Kang *et al.*, 2026). These are transcribed by RNA polymerase I (De Robertis *et al.*, 2020). The DNA for the 5S subunit occurs in tandem arrays (~200–300 true 5S genes and many dispersed pseudogenes), the largest one on the chromosome 1q41-42 (Blokina *et al.*, 2020). 5S rRNA is transcribed by RNA polymerase III (De Robertis *et al.*, 2020). The 18S rRNA in most eukaryotes is in the small ribosomal subunit, and the large subunit contains three rRNA species (the 5S, 5.8S and 28S in mammals, 25S in plants, rRNAs) (Uddin *et al.*, 2015). Pre-rRNA synthesis is regulated by elements including promoters, transcriptional enhancers, and terminators that are located within the ITS (Aubert *et al.*, 2018).

Transcription of rRNA gene arrays results in formation of a nucleolus; consequently, they are termed nucleolar organizer regions (NORs) (De Robertis *et al.*, 2020). Importantly, not all NORs are transcriptionally active and species with multiple NORs can vary the active proportion. Pre-rRNA is matured into 18S, 5.8S, and 28S rRNA by a precisely ordered series of events that includes both cleavages and targeted base modifications (Henras *et al.*, 2015). These are required to ensure correct folding of rRNAs for ribosome assembly and function. These multiple steps in ribosome biogenesis require a bewildering array of proteins and small nucleolar RNAs that converge on transcriptionally active NORs, forming such a high concentration of ribonucleoprotein complexes that nucleoli are the most prominent feature of the eukaryotic nucleus (Jiao, 2023).

In eukaryotes, rRNA genes (found in the nucleolus) are transcribed by RNA Polymerase I into large precursor molecules (like pre-rRNA 45S). This precursor is processed—chemically modified and trimmed to remove spacer sequences—to yield the mature rRNA molecules (e.g., 18S, 5.8S, and 28S in eukaryotes). These mature rRNAs bind to ribosomal proteins to form the small and large ribosomal subunits. These subunits are then exported to the cytoplasm. In the cytoplasm, the small and large ribosomal subunits clamp around an mRNA molecule. The ribosome moves along the mRNA, reading its sequence in triplets (codons). As transfer RNA (tRNA) molecules deliver the correct amino acids based on the mRNA code, the rRNA within the ribosome functions as a ribozyme. It catalyses the formation of peptide bonds between amino acids, linking them into a growing polypeptide chain (Alberts *et al.*, 2022).

History and basics of Nuclear dominance: Nucleolar dominance is an epigenetic phenomenon that occurs in genetic hybrids and describes the expression of 45S rRNA genes inherited from one progenitor due to the silencing of the other progenitor's rRNA genes (Xiao *et al.*, 2016). Nucleolar dominance is a manifestation of rRNA gene dosage control, which also occurs in non-hybrids, regulating the number of active rRNA genes according to the cellular demand for ribosomes and protein synthesis (Neves *et al.*, 2018). Ribosomal RNA gene silencing involves changes in DNA methylation and histone modifications, but the molecular basis for choosing which genes to silence remains unclear (Srivastava *et al.*, 2016). Recent studies indicate a role for short interfering RNAs (siRNAs) or structured regulatory RNAs in rRNA gene silencing in plants or mammals, respectively, suggesting that RNA may impart specificity to the choice mechanism (Puchta-Jasińska *et al.*, 2025). The mechanism is common in occurrence in interspecific hybrids ranging from plants, invertebrates, frogs, flies, fish and mammals. NORs that are active during interphase remain relatively decondensed at metaphase, forming so-called secondary constrictions - the primary constrictions being the centromeres (Mangan *et al.*, 2017). The basis for secondary constriction formation is the persistent binding of Pol I transcription factors that stain intensively with silver (Pilsel *et al.*,

2020). In animals, the Pol I transcription factor, UBF (Upstream Binding Factor) is particularly important for secondary constriction formation. Unlike regions of NORs that were transcriptionally active during interphase, and therefore remain relatively decondensed at metaphase, inactive NORs become fully condensed at metaphase (van Sluis, 2020). This difference in metaphase NOR condensation, which reflects the activity state of the rRNA genes during the preceding interphase, was the molecular basis for the initial discovery of nucleolar dominance as a phenomenon affecting chromosome morphology (Pikaard, 2018).

Historical works on nuclear dominance include earlier work by M.S. Navashin who first documented the phenomenon in *Crepis* (hawkbeard) plant hybrids, naming it "differential amphiplasty". He noticed that in F1 hybrids, chromosomes derived from one species retained their secondary constrictions, while the corresponding regions of the other species completely disappeared (Navashin, 1934). With the rise of molecular biology, researchers Ronald Reeder and others began studying the process in *Xenopus* (clawed frogs). They proposed the "enhancer-imbalance model," which suggests that the dominant species has a higher number of repetitive enhancer sequences in its intergenic spacers, allowing it to titrate and outcompete the recessive species for limiting transcription factors (Reeder, 1985). Studies on chicken cells with two, three, or four NOR-bearing chromosomes synthesize the same amount of rRNA (Muscarella *et al.*, 1987) and maize inbred lines can vary 10- fold in rRNA gene content without displaying differences in growth rate or vigor (Flavell, 1986). Years later Plant biologists such as Craig Pikaard expanded on this, revealing that nucleolar dominance is driven by epigenetics. The silencing is enforced through chromatin modifications—specifically, DNA methylation and histone deacetylation—which turn the repressed parental rRNA genes into inactive heterochromatin (Pikaard, 2000). Dosage control mechanisms were supported by studies such as Sandmeier *et al.*, 2002 which by crosslinking studies showed that only 30%–50% of the rRNA genes in proliferating yeast or murine cells are in an open, psoralen-accessible chromatin structure resulting from active transcription (Sandmeier *et al.*, 2002). Later electron microscopy provided evidences that only half of the approx. 150 yeast rRNA genes are loaded with pol-I elongation complexes (French *et al.*, 2003). In the past decade, an understanding of nucleolar dominance as a large-scale silencing phenomenon has provided additional insights into a chromatin-mediated on/off switch controlling rRNA genes and NORs. Robust epigenetic compensation mechanisms of rDNA expression, through dosage compensation is mediated by a reduction in repressive histone marks and large-scale reorganization of NOR architecture. Available evidence indicates that eukaryotes have more rRNA genes than are required for ribosome biogenesis under most physiological conditions such that they regulate the effective dosage of the rRNA genes they possess. Cells dynamically adjust the proportion of transcriptionally active rDNA units to meet the cellular demands for ribosome production. Epigenetic status of rDNA variants directly determines their spatial partitioning: transcriptionally active, hypomethylated variants are enriched in the nucleolar interior, whereas inactive, hypermethylated variants are sequestered at the nucleolar periphery or in the nucleoplasm. Such spatial partitioning ensures that required rDNA variants are deployed at the appropriate time and location.

Chromatin modifications and role in nucleolar dominance: Nucleolar dominance is an epigenetic phenomenon in which rRNA genes inherited from one parental genome are preferentially transcribed, whereas the corresponding rRNA genes from the other parent are transcriptionally silenced. Because rRNA genes occur as large tandem arrays within nucleolus organizer regions (NORs), nucleolar dominance represents an important example of epigenetic regulation of highly repetitive genomic regions (Chen and Pikaard, 1997; Tucker *et al.*, 2010). Early cytological studies recognized the phenomenon through differential secondary-constriction formation at parental NORs, whereas subsequent molecular analyses established that these cytological differences reflect differential transcription of parental rRNA genes. Thus, nucleolar dominance is now understood primarily as a chromatin-mediated transcriptional regulatory

phenomenon, rather than simply as a structural difference between parental chromosomes. Consistent with this interpretation, active NORs remain relatively decondensed to accommodate transcription, whereas transcriptionally inactive NORs exhibit increased chromatin condensation (Fultz *et al.*, 2023).

DNA methylation and histone modifications: DNA methylation was among the first molecular mechanisms demonstrated to be directly involved in nucleolar dominance. In *Brassica napus*, treatment with the DNA-methyltransferase inhibitor 5-aza-2'-deoxycytidine reactivated normally silent *Brassica oleracea*-derived rRNA genes, demonstrating that the underdominant rDNA is not genetically inactive but is maintained in a methylated, transcriptionally repressed state. Similarly, treatment with histone deacetylase inhibitors such as trichostatin A derepressed normally silent rRNA genes. These experiments established that DNA methylation and histone deacetylation cooperate in maintaining parental rDNA silencing and that the regulatory system extends across large rDNA-containing chromosomal regions (Pikaard *et al.*, 2023). Subsequent work demonstrated that DNA methylation and histone modifications constitute a coordinated epigenetic switch regulating rRNA-gene activity. Lawrence *et al.* (2004) showed that rRNA-gene dosage control and nucleolar dominance involve concerted changes in promoter cytosine methylation and histone modifications. Silenced rRNA genes exhibit increased DNA methylation together with repressive histone modifications, whereas active genes display chromatin characteristics compatible with transcription. Importantly, the study identified the plant histone deacetylase HDT1 as a component of the transcriptional off-switch and demonstrated a self-reinforcing relationship between DNA methylation and histone deacetylation. These findings established that epigenetic repression of rDNA is not dependent on a single chromatin modification but instead involves interconnected mechanisms that stabilize the inactive state (Lawrence *et al.*, 2004). Histone acetylation provides an additional level of control over rRNA-gene accessibility. In *Arabidopsis suecica*, RNA-interference screening identified HDA6 as a histone deacetylase required for nucleolar-dominance-associated rRNA-gene silencing. Loss of HDA6 activity resulted in depression of normally silent rRNA genes and was accompanied by NOR decondensation, loss of promoter cytosine methylation, and replacement of repressive histone marks such as H3K9 dimethylation with transcription-associated modifications, including increased histone acetylation and H3K4 trimethylation (Earley *et al.*, 2006). These findings indicate that histone deacetylation contributes directly to the establishment and maintenance of the inactive rDNA state rather than simply representing a consequence of transcriptional repression.

Small RNA-directed DNA methylation: The epigenetic regulation of nucleolar dominance is further reinforced by small RNA-mediated pathways. Preuss *et al.* (2008) demonstrated that the RNA-directed DNA methylation (RdDM) machinery is required for efficient silencing of the underdominant rRNA genes in *A. suecica*. Their RNA-interference screen identified DRM2, together with the methylcytosine-binding proteins MBD6 and MBD10, as components required for nucleolar dominance. Moreover, disruption of RDR2 or DCL3, which participate in siRNA biogenesis, impaired rRNA-gene silencing. These results support a model in which siRNAs derived from rDNA-associated sequences guide de novo DNA methylation through DRM2, after which methylcytosine-binding proteins contribute to the maintenance of the repressed state across large rDNA arrays (Preuss *et al.*, 2008). More recent studies have expanded the significance of RNA-mediated regulation beyond hybrid-specific nucleolar dominance. Shatskikh *et al.* (2024) summarized evidence that RNA interference pathways participate in rDNA transcriptional regulation, chromatin silencing, and maintenance of rDNA integrity in diverse eukaryotic systems. These observations suggest that the small-RNA machinery involved in nucleolar dominance is likely related to a broader cellular system for controlling the transcriptional output of multicopy rDNA arrays. However, because much of this recent evidence concerns general rDNA regulation rather than parental rDNA discrimination in hybrids, the contribution of small RNAs should be interpreted as a component of the epigenetic

machinery underlying nucleolar dominance, rather than as an independently sufficient explanation for parental specificity (Shatskikh *et al.*, 2024).

A major conceptual development in the field is the recognition that nucleolar dominance may be regulated at a scale considerably larger than individual rRNA-gene promoters. Classical models emphasized sequence differences between parental rRNA genes and differential recognition by transcriptional regulators. However, recent analyses indicate that the NOR and its chromosomal context can constitute an important regulatory unit. Pikaard *et al.* (2023) proposed that the mechanisms responsible for nucleolar dominance may operate across multi-megabase regions, with the transcriptional state of rRNA genes influenced by the NOR in which they reside rather than being determined solely by the nucleotide sequence of individual rRNA genes. This model provides an explanation for the coordinated silencing of large parental rDNA arrays following hybridization (Pikaard *et al.*, 2023). Additionally, NOR-scale model is further supported by recent advances in the characterization of repetitive DNA. Mo *et al.* (2023) developed single-molecule targeted accessibility and methylation sequencing (STAM-seq) to simultaneously examine DNA methylation and chromatin accessibility in highly repetitive genomic regions, including *Arabidopsis* rDNA. Their analysis demonstrated an inverse relationship between DNA methylation and accessibility at individual rDNA units and showed that DNA methylation-deficient mutants exhibit increased chromatin accessibility. These findings provide additional evidence that DNA methylation is closely associated with the chromatin accessibility state of rDNA and illustrate how long-read and single-molecule approaches can resolve epigenetic heterogeneity within repetitive rDNA arrays.

Collectively, these studies suggest that nucleolar dominance should not be viewed simply as the independent repression of thousands of nearly identical rRNA-gene copies. Instead, DNA methylation, histone modifications, small RNA pathway and chromatin accessibility may establish coordinated epigenetic states across large portions of an NOR. Such organization would provide an efficient mechanism for regulating rRNA-gene dosage because the transcriptional state of an entire array or chromosomal domain could be modulated without requiring independent regulation of every repeat. This interpretation also helps reconcile the classical observation of parental NOR dominance with more recent evidence for chromosomal-context-dependent regulation.

Role of smallRNA (sRNA) in Nuclear dominance: The study of how long noncoding RNAs (lncRNAs) affect chromatin structure and epigenetic regulation of transcription is one of the most intriguing findings from RNA research (Ávila-Avilés *et al.*, 2025). The number of mammalian lncRNAs is continuously expanding, and functional investigations have improved our comprehension of their functions in controlling gene expression. Research implicates that many of these ncRNAs are antisense RNAs that overlap coding regions or cluster close to the 5' or 3' terminal regions of genes (Poliseno *et al.*, 2024). RNA is especially well adapted for the task of specific recognition of other RNAs and genomic loci because of its base complementarity rendering RNA incredibly sequence-specific (Lu *et al.*, 2018). The need for protein synthesis and, metabolic activity determines a cell's total rDNA transcriptional activity. However, only a portion of rDNA copies are transcribed, and other repeats are silenced in a cell and/or tissue-specific manner, even in cycling cells with high rRNA synthesis activity (Bierhoff *et al.*, 2013). Transcriptionally active and silent rRNA genes in mammals are distinguished by a number of epigenetic characteristics. By directing targeted DNA methylation and histone modification, small RNAs—especially, siRNAs and snoRNAs—play a fundamental role in epigenetic mediated nuclear silencing (Bure *et al.*, 2022). Generally, an “open” chromatin structure that is characterized by DNA hypomethylation, acetylation of histone H4 (H4ac) and dimethylation of histone H3 at lysine 4 (H3K4me2). These marks are “labels” of transcriptionally active gene promoters, whereas silent rDNA repeats are characterized by promoter hypermethylation, histone H4 hypoacetylation, and

methylation of H3K9, H3K27, and H4K20 (Yu *et al.*, 2015). At the active rRNA genes, the promoter of transcriptional permissive, "poised" genes is unmethylated (Zhao *et al.*, 2016), further it is associated with components of the preinitiation complex. The promoter-bound nucleosome carries both euchromatic (H3K4me3) and heterochromatic (H3K27me3) histone modifications (Igolkina *et al.*, 2019). Active and silent rDNA repeats are characterized by distinct nucleosome positions. Centromeres are specialized chromosomal structures that govern kinetochore assembly and ensure equal chromosome segregation during mitosis (Li *et al.*, 2006). They create enormous arrays up to several megabases and are made up of short tandem repetitions. Kinetochore function and chromosomal integrity depend on maintaining a heterochromatic structure at centromeres (Koch *et al.*, 2025). The 171-bp α -satellite repeats that make up human centromeres are encircled by arrays of longer repeating elements, such as satellites II and III (Sat II and III), which are scattered with distinct sequence elements (Showman *et al.*, 2021). A distinct chromatin signature in the core region, includes the centromere-specific histone H3 variation CENP-A (Jeffery *et al.*, 2022) and a nucleoprotein complex incorporating additional centromeric proteins (Rakshit *et al.*, 2020) which determine centromere identity epigenetically. Nucleosomes carrying H3K4me2 regularly disrupt chromatin containing CENP-A (Molina *et al.*, 2016), while heterochromatic histone modifications, such as di- and trimethylated H3K9 and H4K20 as well as related HP1 proteins, characterise the adjacent pericentromeric heterochromatin (Fioriniello *et al.*, 2020). Numerous centromeric proteins feature a nucleolar targeting domain, and centromeres have been found to localize around nucleoli. This suggests that the nucleolus, which serves as a centre for heterochromatin formation and ncRNA-dependent gene regulation, may be involved in kinetochore assembly (Schöfer *et al.*, 2018). Actually, it seems that the same mechanisms that silent rDNA also mediate heterochromatin formation at centric and pericentric repetitions, with NoRC being a key player in this process. Nucleolus organiser regions (NORs) are tandemly arranged clusters of several hundred copies of rRNA genes (rDNA) found in mammalian genomes (Bersaglieri *et al.*, 2019). Multiple copies of rRNA genes are carried by interspecific hybrids (as in some *Arabidopsis species*) in areas known as Nucleolus Organiser Regions (NORs) (Mohannath *et al.*, 2016). A successive short RNA mechanism is necessary to silence the subordinate species' NOR. The mechanism involves the transcription of intergenic subordinate NOR's non-coding sequences (Palos *et al.*, 2022). Next Dicer-like (DCL) enzymes convert these transcripts into 24 nucleotides long small interfering RNAs (siRNAs). The Argonaute proteins and DNA methyltransferases (such as DRM2) are directed to the subordinate rRNA promoters by siRNAs (Sigman *et al.*, 2021). The subordinate genes are then forced into dense, transcriptionally silent heterochromatin as a result of this localisation, which causes *de novo* DNA methylation and histone modifications (such as deacetylation by enzymes like HDA6) (Hamali *et al.*, 2023). In order to direct particular proteins to regulatory genomic loci or to substitute them from their target sequence, noncoding RNAs (ncRNAs) attached to regulatory gene sequences by Hoogsten base pairing serving as a "local address." (Li, 2023) A considerable portion of NoRC is linked to pericentromeric chromatin, according to TIP5 (the major subunit of NoRC) localisation analysis using ChIP assays and immunostaining (Kresoja-Rakic *et al.*, 2019). Experimental evidences indicate while TIP5 overexpression raised the amount of heterochromatic histone marks, TIP5 depletion decreased H3K9me3 and H4K20me3 at key satellite repeats (Dalcher *et al.*, 2019; Ciccarone *et al.*, 2017). The integrity of heterochromatin at centromeres is protected by a balanced, low-level synthesis of satellite transcripts and differential expression in a developmental or tissue-specific manner (Grewal *et al.*, 2023; Subirana *et al.*, 2023). Because their sequence overlaps the rDNA promoter, spacer transcripts are processed into a diverse population of 150–250 nt RNAs known as pRNA (promoter-associated RNA) (Vydzhak *et al.*, 2020). A phylogenetically conserved hairpin shape allows pRNA to interact with TIP5, the major subunit of NoRC (Anosova *et al.*, 2015). To attract NoRC to nucleoli, pRNA and TIP5 must interact. Notably, refeeding with ectopic pRNA restored nucleolar localisation, while depletion of pRNA induced NoRC to translocate from nucleoli to the nucleoplasm (Gupta *et al.*, 2020). This highlights the crucial

role of pRNA in directing NoRC to rDNA and creating the repressive chromatin structure. While transfection of cells with synthetic pRNA caused *de novo* methylation of the rDNA promoter and suppressed transcription (Ma *et al.*, 2023), depletion of pRNA reduced DNA methylation and increased rDNA transcription (Yang *et al.*, 2024). Crucially, irrespective of the NoRC complex, the 5'-end of pRNA can cause rDNA silencing and promoter hypermethylation (Vydzhak *et al.*, 2020). Hoogsten base pairing between pRNA and the rDNA promoter accomplishes this by creating a triple-stranded DNA-RNA structure at the transcription factor TTF-I binding site (Pirogov *et al.*, 2019). Transcriptional repression is started when TTF-I is displaced from its corresponding site T0 by the triple-helical DNA: RNA structure (Kohestani *et al.*, 2023). The *de novo* DNA methyltransferase DNMT3b can then precisely identify the triplex, resulting in the methylation of a crucial CpG residue (Elliott *et al.*, 2026). This methylation hinders the transcription factor UBF's ability to bind and stops transcription complex assembly (Theophanous *et al.*, 2023). Studies reveal a new mode of epigenetic regulation: the loading CEN proteins, such as INCENP, Survivin, and aurora B kinase, to centromeres requires transcripts from minor and α -satellite repeats (Chandra C., 2024). Furthermore, it has been demonstrated that single-stranded RNA binds to CENP-C and improves its binding to DNA (Leclerc *et al.*, 2021). Centromeric transcription was lost and the CENP-A chaperone HJURP was mislocalized when the lysine demethylase LSD1 demethylated H3K4me2 (Bergmann *et al.*, 2020). However, centromere inactivation and failure to recruit CENP-A were caused by acetylation of H3K9 and overexpression of satellite RNA, underscoring the role of RNA in the protein composition and epigenetic characteristics of centric chromatin (Sharma *et al.*, 2019). RNA is also a structural component of pericentric heterochromatin, and the localisation of HP1 α and H3K9me3 at centromeres depends on RNA-protein interactions (Akram *et al.*, 2018). Furthermore, the SUMO-modified version of HP1 α selectively binds to large satellite transcripts, facilitating HP1 α loading to pericentric heterochromatin, according to a recent investigation of HP1 α binding to RNA (Maison *et al.*, 2016). In response to heat shock, DNA damage, or osmotic stress, pericentric heterochromatin has been demonstrated to develop euchromatic characteristics that facilitate the transcription of RNAs containing a subset of Sat III repeats (Fonseca-Carvalho *et al.*, 2024). Nuclear stress bodies (nsBs), which contain RNAP II along with transcription and splicing factors, are formed by the Sat III transcripts (Chatterjee *et al.*, 2021). Satellite repression depends on both DNA methylation and H3K9 trimethylation, and dysregulation of these epigenetic markers is associated with the development of cancer. A massive production of bidirectional ncRNAs from large satellite repeats in cancer cells was discovered by digital gene expression analysis, indicating that global changes in pericentric RNAs may impact differentiation programs linked to cancer (Hashimoto *et al.*, 2015). TERRA (telomeric repeat-containing RNA) are ncRNA that are actively transcribed from telomeres (Chebly *et al.*, 2022). TERRA transcription starts at a promoter-like CpG island in subtelomeres and moves toward the ends of chromosomes. siRNA-mediated TERRA knockdown reduced H3K9me3 at telomeric chromatin (Zeng *et al.*, 2017) and triggered a large DNA damage response at telomeres, supporting TERRA's impact on telomere structure (Rivosecchi *et al.*, 2024). These findings show that TERRA affects the formation and/or upkeep of the restrictive chromatin structure at chromosomal ends, a process that is disrupted in telomere-related disorders like cancer and early ageing (Sinha *et al.*, 2015). In order to create heterochromatic features at telomeres, NoRC binds to a sizable portion of them and attracts histone-modifying enzymes including Suv4-20h2 and SIRT6 (Mangiavacchi *et al.*, 2023). In knockout experiments TIP5 knockdown had the opposite effect, overexpression of TIP5 raised the levels of H3K9me3 and H4K20me3 (Zhang *et al.*, 2024) and reduced the acetylation of histone H4 at telomeres and subtelomeres (Episkopou *et al.*, 2024). Interestingly, TIP5 overexpression or removal caused comparable changes in TERRA levels, suggesting that NoRC works with TERRA to maintain the structural and functional integrity of telomeres (Feretzaki *et al.*, 2019). Retrotransposition in the germline would have negative effects, suggesting the requirement for a particular defence mechanism, since the genomic integrity of germ cells is essential for the transfer of genetic information to the following generation (Wang, 2017).

Table 1. A brief list of nuclear dominance in grasses

Taxon	Short characteristics	Dominant	Underdominnat	Method/ Reference
<i>Avena barbata</i>	Tetraploid AABB	AA	BB	Silver staining, FISH Irigoyen <i>et al.</i> 2001
<i>Brachiaria decumbens</i>	Tetraploid cv. Basilisk, B1 B1 B2 B2	Unknown	Unknown	Silver staining, FISH Carrilho <i>et al.</i> 2012
<i>Elymus tetraploids</i>	Tetraploid SSHH	SS	HH	Silver staining 96. Mason-Gamer <i>et al.</i> , 1992
<i>Lolium multiflorum</i>	cv. Barjumbo (4x) and cv. ABARP (3x)	Unknown	Unknown	Silver staining, FISH Bustamante, <i>et al.</i> , 2014
<i>T. aestivum</i> × <i>Secale cereale</i>	cv. Chinese Spring × cv. Centeio do Alto (F1 hybrid, ABDR	1B and 6B	1R	Silver staining, 9. Vieira <i>et al.</i> , 1990
<i>Z. mays</i> inbred line	Intraspecific F1 hybrid Sx19 (♀ B73 × ♂ Mo17)	B73-derived rDNA	Mo17- derived Rdna	Silver staining, RNA slot blot 22. Jupe <i>et al.</i> , 1993

Table- 2. List of various proteins associated with nuclear dominance

Protein	Function	Reference
RNA Polymerase I (Pol I)	Transcribing 45S pre-rRNA at the nucleolar organizer regions (NORs)	Chen,2025
Upstream Binding Factor (UBF)	Transcription factor that binds to rDNA promoters and enhancer elements,	Duployez <i>et al.</i> , 2023
Selectivity Factor 1 / Transcription Initiation Factor IA (SL1/TIF-IB):	Interacts with UBF and Pol I to position the initiation complex correctly on the rRNA gene promoter.	Gorski <i>et al.</i> , 2007
DNA Methyltransferases (e.g., DNMT1, DNMT3a/3b)	Mediate the heavy cytosine DNA methylation that characterizes the inactive/silenced rDNA repeats in mammals	Li <i>et al.</i> , 2016
Histone Deacetylases (HDACs)	Histone deacetylation, compacting the chromatin structure of the underdominant or silenced ribosomal genes	Xu <i>et al.</i> , 2021
Methyl-CpG-Binding Proteins (e.g., MeCP2, MBD proteins)	Recognize methylated DNA at silenced rDNA promoters to recruit corepressor	Ravi <i>et al.</i> , 2025

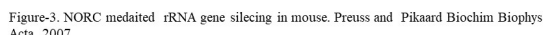
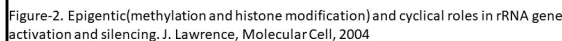
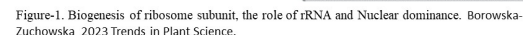
Table-3. Major differences in the mechanisms and pathways of plant and animal nuclear dominance

Function	Plant	Mammal	Reference
Regulatory Mechanisms	short interfering RNAs (siRNAs)	structured regulatory RNAs	Lawrence, 2004
	histone deacetylases (like HDT1)	competitively titrated by intergenic spacer subrepeats	Tucker, 2010
Occurrence and Ploidy	Widespread	Much rarer to study naturally due to developmental and reproductive barriers to hybridization	Ma <i>et al.</i> , 2005
	extensively studied in allopolyploids	specific animal models and rare polyploid rodents	Gallardo <i>et al.</i> , 2006
RNA-Targeting Specificity	rely on small interfering RNAs (siRNAs) and RNA-directed DNA methylation (RdDM) pathways	structured regulatory non-coding RNAs and specialized chromatin-remodeling complexes like the Nucleolar Remodeling Complex	Finigan <i>et al.</i> , 2008
Protein Machinery Divergence	Use specific remodelers and methyl-CpG-binding domain (MBD) proteins	Utilize mammalian-specific upstream factors and promoter-competition dynamics	Volkov <i>et al.</i> , 2004.
Core Similarities	Both use DNA methylation and histone deacetylation	Both use DNA methylation and histone deacetylation	El-Osta <i>et al.</i> , 2018
	RNA Polymerase I transcription is selectively blocked at the Nucleolar Organizer Regions (NORs)	RNA Polymerase I transcription is selectively blocked at the Nucleolar Organizer Regions (NORs)	Goodfellow <i>et al.</i> , 2013

In quiescent cells, transcripts from IAP and LINE-1 elements seem to cause chromatin compaction and H4K20 trimethylation to be upregulated (Bonitto *et al.*, 2021). These findings suggest that RNA derived from retroelements acts as a signal to attract Suv4-20h2 and create a repressive chromatin structure at these repeating sequences. Furthermore, in human cells, bidirectional transcripts from LINE-1 elements produce short interfering RNAs that cause an RNA interference response that inhibits transposition (Liu *et al.*, 2026).Primarily produced in germ cells, the PIWI clade of Argonaute proteins interacts with 24–30 nucleotide-sized RNAs (piRNAs) to form a piRNA-induced silencing complex known as piRISC (Haase *et al.*, 2022).Because these piRNA clusters contain a variety of transposable elements, piRISC-mediated transposon inhibition occurs at both the transcriptional and posttranscriptional levels (Onishi *et al.*, 2021). Male germ cells in mice exhibit three PIWI-like proteins: MILI, MIWI, and MIWI2 (Wei *et al.*, 2024). Each of these proteins plays a crucial function in spermatogenesis, as evidenced by the male-specific sterility caused by their knockout.

A stretch of polypurine residues within the ORF1 region that may form a DNA:RNA triplex structure was found when a LINE-1 element's sequence was analysed (Herbert, 2026). Nuclear staining of late 2-cell embryos was demonstrated by immunofluorescence using an antibody that recognises triple helices (Bogolyubova *et al.*, 2023). At the 8-cell stage, staining was nearly undetectable, indicating that transcriptional activation of LINE-1 elements happens in a limited amount of time during early development. These findings collectively imply that repeated elements have the ability to autoregulate their activity by producing short RNAs that modify the epigenetic state of the target sequences (Castel *et al.*, 2013).

Nucleolar dominance as a manifestation of rRNA gene dosage control: Eukaryotic genomes contain hundreds to thousands of tandemly repeated rRNA genes, although only a proportion of these copies is transcriptionally active at a given time. This arrangement

[illegible]

The relationship between rDNA dosage and nucleolar function is also evident from recent studies of rDNA maintenance. Hori *et al.* (2023) highlighted that cells actively regulate rDNA copy number through mechanisms controlling recombination, replication, and genome stability, while RNA polymerase I activity adjusts rRNA production from the available gene pool. Therefore, rRNA homeostasis involves at least three interconnected levels: maintenance of the physical rDNA complement, selection of transcriptionally competent genes, and regulation of transcriptional output. Nucleolar dominance can be incorporated into this framework as a specialized situation in which parental rDNA arrays become differentially selected for transcription following genome merger. Recent reviews of selective rRNA-gene repression in plants further support this interpretation. They emphasize that nucleolar dominance is accompanied by coordinated epigenetic changes and that advances in long-read sequencing are revealing considerable structural and epigenetic heterogeneity within rDNA arrays (Pontvianne *et al.*, 2023). Consequently, the active rDNA complement should be viewed as a dynamic population of genes rather than as a uniform block of identical repeats. This

provides a mechanistic basis for adjusting rRNA production without requiring changes in total rDNA copy number. Overall, the available evidence indicates that nucleolar dominance represents an extreme and experimentally visible form of rRNA-gene dosage control. Genome hybridization increases the potential rDNA dosage, whereas selective transcriptional repression limits the number of parental rRNA genes contributing to ribosome production. The balance between rDNA copy number, epigenetic state, NOR organization, and RNA polymerase I activity therefore determines the functional rRNA-gene dosage. This interpretation connects nucleolar dominance with the broader cellular requirement to maintain adequate ribosome production while avoiding unnecessary transcription of the complete rDNA complement (McStay, 2006; Pontvianne *et al.*, 2012; Hori *et al.*, 2023; Pikaard *et al.*, 2023).

RNA and chromatin-dependent rRNA gene silencing in mammals: Ribosomal RNAs (rRNAs) are the most prevalent RNAs in cells, and are produced from rDNA repeats by RNA Polymerase I accounts for the bulk of all transcription (Antony *et al.*, 2022). rRNA represents approximately 80% of the total RNA in proliferating mammalian cells. Cells evolved a unique transcription system by employing an efficient RNA polymerase machinery and amplifying the number of rRNA genes to hundreds or even thousands of copies per genome in order to meet the massive demand for ribosome biosynthesis. These factors make rDNA as the “king of the housekeeping genes” in terms of both function and quantity (Liu *et al.*, 2018). The upstream binding factor UBF and the TBP-TAFI complex SL1, often referred to as TIF1B, are two additional basal factors that are necessary for the transcription of rRNA genes by RNA Polymerase I (Pol I) (Griesenbeck *et al.*, 2017). The high density of Pol I on rRNA genes indicates that transcription of rRNA genes is highly effective. Therefore, it is evident that the presence of numerous rRNA genes that transcribe at such fast rates clearly contributes to the production of high levels of rRNA (Moss *et al.*, 2019). Humans and mice have about 200 rRNA genes per haploid genome, however the number of rRNA gene repetitions varies greatly throughout phylogeny (Tsekrekou *et al.*, 2017). Nucleolar organizer regions (NORs) are chromosomal regions that contain rRNA genes. NORs in human cells vary in size from 50 kb to more than 6 Mb (Mangan *et al.*, 2017). During mid-late S-phase, when heterochromatic DNA is typically replicated and inherited during cell division, the silent rRNA genes replicate. The presence of CpG methylation at the rRNA gene promoter abrogates the formation of the Pol I pre-initiation complex. UBF binding is hampered by methylation of CpG at position –133 of the mouse rDNA promoter. Accordingly, in mouse or human cells, UBF does not bind to the promoter of silent rRNA genes (Bersaglieri *et al.*, 2019). The RNA-dependent recruitment of the Nucleolar Remodeling Complex (NoRC) is one of the best-characterized mechanisms of mammalian rRNA gene silencing. Promoter-associated RNA (pRNA), transcribed from the rDNA intergenic spacer, interacts with the TIP5 subunit of NoRC, directing the complex to rDNA promoters. In the end, this recruitment stops RNA Polymerase I from accessing the promoter by starting ATP-dependent chromatin remodeling, histone deacetylation, DNA methylation, and the creation of repressive heterochromatin. As a result, transcriptionally silent rDNA repeats are stably maintained across cell divisions (Vyzhzhak *et al.*, 2020).

In mammalian cells, rRNA genes can be classified into three major classes according to the transcriptional state and chromatin and epigenetic features: silent, inactive (or pseudogenes), and active genes. In somatic cells, the presence of DNA methylation at the promoter region distinguishes silent rRNA genes from the rest of the repeats (Santoro *et al.*, 2001). According to Zhou *et al.* (2002), silent rRNA genes have heterochromatic structures and are associated with repressive histone marks like H3K9me2, H3K9me3, and deacetylated histones. It is possible to further categorize the remaining rRNA genes in mammalian cells that are not included in the silent fraction as either active or inactive genes. The lack of DNA methylation in these repetitions suggests that their transcription status may be potentially reversible. UBF is the primary key factor involved in the formation of both active and inactive rRNA genes (Hamdane *et al.*, 2014; Herdman *et al.*, 2017). In the coding area, active genes are

nucleosome-free and bind to UBF. UBF's interaction with the rRNA gene body, spacer promoter, and enhancer repeats enables the creation of the pre-initiation complex (PIC), which is followed by RNA Pol I loading and rRNA transcription. Inactive genes are a component of the nucleosome-packed rDNA chromatin and do not interact with UBF, in contrast to silent rRNA genes. UBF depletion converts active genes into inactive chromatin by promoting histone H1-induced assembly of transcriptionally inactive chromatin. Crucially, the active gene number is restored with recovery of UBF expression, suggesting that the transition from an active to an inactive state may be reversible (Theophanous *et al.*, 2023). The active or silent states of rDNA repeats in the synthesis of rRNA in mammals are strictly controlled by diverse metabolic pathways, environmental factors, and cell cycle stages. The integrity of the rDNA genome in mammals depends on the maintenance of rDNA chromatin silencing, which prevents aberrant homologous recombination within sister chromatids and keeps the rDNA in a condensed, transcriptionally refractory state. Thus, loss of silencing at rDNA loci correlates with rDNA instability, nucleolar disintegration, or even cellular senescence as well as with many types of diseases (Khan *et al.*, 2015; Srivastava *et al.*, 2016). Recent studies have expanded this regulatory framework by identifying additional long non-coding RNAs (lncRNAs), antisense transcripts, RNA-binding proteins, and chromatin modifiers that coordinate nucleolar organization and rRNA gene expression. Furthermore, rDNA regulation is extremely dynamic and responsive to developmental cues, nutrition availability, cellular stress, aging, and disease, according to developments in high-throughput sequencing, chromatin profiling, CRISPR-based epigenome editing, and single-cell genomics (Statello *et al.*, 2020). Transcriptionally active and silent rRNA genes in mammals are distinguished by a number of epigenetic characteristics. Transcriptionally active gene promoters are typically identified by a “open” chromatin structure that is marked by DNA hypomethylation, acetylation of histone H4 (H4ac), and dimethylation of histone H3 at lysine 4 (H3K4me2), while silent rDNA repeats are marked by promoter hypermethylation, histone H4 hypoacetylation, and methylation of H3K9, H3K27, and H4K20 (Santoro *et al.*, 2002). Similar to active rRNA genes, the promoter of these transcriptional permissive, “poised” genes is unmethylated and linked to preinitiation complex components; however, the promoter-bound nucleosome contains both heterochromatic (H3K27me3) and euchromatic (H3K4me3) histone modifications (Potabattula *et al.*, 2025).

Illustration of rDNA silencing pathways in mammals: First, the ATPase SNF2h (sucrose-nonfermenting protein 2 homolog) and the DNA-binding protein TIP5 (transcription termination factor I [TTF-I]-interacting protein 5) make up the NoRC (nucleolar remodeling complex), an ATP-dependent chromatin-remodeling complex that belongs to the ISWI/SNF2h family (Malik *et al.*, 2025). By coordinating various histone-modifying enzymes, DNMTs, or promoter-associated RNA (pRNA), a small intergenic noncoding transcript necessary for NoRC-mediated heterochromatin formation, this complex creates rDNA silencing by preventing the formation of a transcription initiation complex at the rDNA promoter (Levesque *et al.*, 2025). In order to prevent the assembly of transcription complexes and achieve rDNA silence, the NoRC facilitates a shift of the nucleosome to a repressive/inactive location 25 nucleotides (nt) downstream with regard to the transcription start site. (Feng *et al.*, 2016). Furthermore, the establishment of a quiet rDNA chromatin structure depends on the NoRC's interaction with the rDNA promoter, and the NoRC's binding to the rDNA promoter via TTF-I attracts histone- or DNA-modifying proteins like HDAC1 (histone deacetylase 1), DNMT1, or DNMT3b. Specifically, by binding with histone H4 acetylated at lysine 16 (H4K16ac) and subsequently enabling HDAC1-mediated deacetylation of histone H4 at the K5, K8, and K12 residues, the bromodomain within TIP5 contributes significantly to NoRC-mediated rDNA silencing (Zhou *et al.*, 2002; Ray *et al.*, 2021). Second, SIRT1, the histone methyltransferase SUV39H1 (also called KMT1A), and a nucleolar protein called NML (nucleomethylin) make up the eNoSC (energy-dependent nucleolar silencing complex). These complex shields mammalian cells from energy-deprivation-dependent apoptosis and mediates rDNA silencing in response to glucose starvation. Elevation of the

NAD⁺/NADP⁺ ratio initiates SIRT1 deacetylase activity for histone H3 at rDNA promoters, hence enhancing energy-dependent rDNA transcriptional repression (Mirza *et al.*, 2024). Third, two types of catalytic subunits, such as HDAC1/2 and the ATP-dependent helicase CHD3/4, and nonenzymatic proteins, such as GATA zinc finger domain-containing proteins 2A and 2B (GATAD2A/2B), methyl-CpG-binding domain proteins (MBD2/3), metastasis-associated proteins (MTA1/2/3), and retinoblastoma-binding proteins (RBBP7/4) (Allen *et al.*, 2013). The reduction of cell development triggers the activation of the NuRD complex, which creates the poised state of rDNA, a chromatin state that is accessible to transcriptional factors but transcriptionally inactive. This maintains the dormant rDNA and inhibits rDNA transcription. When TTF-I attaches to the T0 element and the DNA-dependent ATPase CSB (Cockayne syndrome protein B), the NuRD complex is more readily recruited to unmethylated CpG rDNA promoters. It's interesting to note that the NuRD complex also suppresses CpG methylation at rDNA promoters by negatively regulating TIP5 expression. In order to maintain silent rDNA in growth-arrested or differentiated cells, the NuRD complex-mediated state of rDNA can be classified as either a poised state of rDNA chromatin or of rRNA genes (Xie *et al.*, 2012). By creating a repressive nucleosome on the rDNA core promoter, which is linked to bivalent histone modifications; a heterochromatic mark, trimethylated histone H3 at lysine 27 (H3K27me3); a euchromatic mark, trimethylated histone H3 at lysine 4 (H3K4me3); and an intermediate configuration of rDNA chromatin, the NuRD complex maintains this poised state of rDNA chromatin (Srivastava *et al.*, 2016).

RNA and chromatin-dependent rRNA gene silencing in plants: In plants, rRNA gene silencing is controlled by a complex interplay between chromatin modifications, DNA methylation, histone modifications, ATP-dependent chromatin remodeling, and non-coding RNAs. In contrast to mammals, plants have an extra regulatory mechanism called RNA-directed DNA methylation (RdDM), which uses small interfering RNAs (siRNAs) to control heterochromatin formation and sequence-specific DNA methylation. This pathway provides a unique mechanism by which RNA molecules directly influence chromatin structure and transcriptional silencing of repetitive genomic regions, including rDNA (Zhang, *et al.*, 2026). One of the most remarkable examples of RNA- and chromatin-mediated rRNA gene regulation in plants is nucleolar dominance, an epigenetic phenomenon observed in many interspecific hybrids and allopolyploids. During nucleolar dominance, the entire set of rRNA genes inherited from one parental species is selectively silenced, while the homologous genes from the other parent remain transcriptionally active. This parent-specific silencing is reversible and is established through coordinated actions of DNA methyltransferases, histone deacetylases, histone methyltransferases, chromatin-remodeling complexes, and RNA-dependent silencing pathways (Borowska-Zuchowska *et al.*, 2023). Each rDNA repeat in *Arabidopsis* is around 10 kb in size, and each haploid genome contains between 570 and 750 copies. The *Arabidopsis* rRNA gene clusters, also known as NORs and found on the short arms of chromosomes 2 and 4 (NOR2 and NOR4, respectively), are comparable to human rDNA repeat clusters (Dvorackova *et al.*, 2015). The rRNA genes derived from *A. thaliana* are silenced in *Arabidopsis suecica*, an allotetraploid hybrid of *A. thaliana* and *A. arenosa*. In *A. suecica*, transgene-induced RNA interference (RNAi) has shown promise as a method for pinpointing particular chromatin-modifying activities necessary for nucleolar dominance (Earley *et al.*, 2006). HDT1 and HDA6 were found to be necessary for rRNA gene silencing in nucleolar dominance through systematic knockdown of the sixteen predicted histone deacetylases. The de novo methyltransferase DRM2 is necessary for the silencing of the rRNA genes derived from *A. thaliana* in the hybrid, according to similar experiments that target the predicted DNA methyltransferases (Tucker *et al.*, 2010; Earley *et al.*, 2010). Similarly, MBD6 and MBD10 were required when the twelve anticipated methylcytosine binding domain proteins were knocked down. MBD6 predominantly colocalizes with rRNA gene loci, while MBD10 localizes throughout the nucleus (Tucker *et al.*, 2010; Ichino *et al.*, 2021). Nucleolar dominance, a phenomenon where rRNA genes of one species are transcriptionally dominant over rRNA genes of other species, governs

rRNA gene silencing in *Arabidopsis*. Nucleolar dominance in plants is regulated epigenetically because it requires HDA6 and DRM2, which are homologs of mammalian Rpd3 deacetylase and DNMT3b, respectively. This is noteworthy because the regulation of nucleolar dominance in plants is similar to that of NoRC-mediated rDNA silencing in mammals. The function of mammalian pRNA in controlling rDNA silencing is similar to that of short interfering RNA (siRNA) produced from IGS of the *Arabidopsis* rRNA gene (Pikaard *et al.*, 2023). In addition, it was recently shown that all silenced rRNA gene subtypes map to NOR2, whereas all active rRNA gene subtypes map to NOR4 in *Arabidopsis*, suggesting that selective rRNA gene silencing is not regulated by gene-based mechanisms but by a subchromosomal silencing mechanism (Rabanal *et al.*, 2017). The RNA-directed DNA methylation pathway plays a central role in this process. In this pathway, specialized RNA polymerases (Pol IV and Pol V), Dicer-like proteins (DCLs), Argonaute proteins (AGOs), RNA-dependent RNA polymerases (RDRs), and 24-nucleotide siRNAs cooperate to recruit DNA methyltransferases to homologous rDNA loci. The resulting cytosine methylation, together with histone H3 lysine 9 dimethylation (H3K9me2) and chromatin condensation, establishes stable heterochromatin that prevents RNA Polymerase I from initiating rRNA transcription (Erdmann *et al.*, 2020).

rRNA biology and its application: Recent advances in genomics and epigenetics have revolutionized plant breeding and biotechnology, providing innovative approaches for crop improvement under changing climatic conditions. Plant epigenetics, in particular, offers significant potential for developing high-yielding and stress-resilient crops (Chen, 2025). Emerging evidences into nucleolar dominance, genomic imprinting, paramutation, RNA silencing, and transgenerational epigenetic inheritance have expanded our understanding of epigenome-mediated regulation in plants. A well-characterized example of epigenetic regulation is the *Vgt1* flowering-time quantitative trait locus (QTL) in maize, where a non-coding cis-regulatory element located upstream of an AP2-like transcription factor controls flowering time through transposon-associated DNA methylation (Castelletti *et al.*, 2014). This example demonstrates how epigenetic modifications at cis-regulatory regions modulate gene expression and contribute to phenotypic variation. Collectively, the coordinated action of cis-regulatory elements and trans-acting factors has emerged as a fundamental mechanism governing natural variation, tissue-specific gene expression, developmental plasticity, and environmental adaptation in plants (Marand *et al.*, 2023). Another important application involves the identification and utilization of stable epialleles and epigenetic quantitative trait loci (epiQTLs) associated with agronomically important traits. Integrating these epigenetic markers into marker-assisted selection and genomic selection programs offers new opportunities to improve drought tolerance, yield stability, and resource-use efficiency in crop plants (Kakoulidou *et al.*, 2021; Verkest *et al.*, 2015). Progressive studies in CRISPR/dCas9-based epigenome editing have further expanded the scope of epigenetic breeding by enabling precise modification of DNA methylation and chromatin states at stress-responsive loci without altering the genome sequence (Tadić *et al.*, 2020). When integrated with conventional breeding, genomic selection, and modern biotechnology, these approaches provide a comprehensive framework for developing high-yielding, climate-resilient, and stress-tolerant crop varieties capable of sustaining agricultural productivity under changing environmental conditions (Turcotte *et al.*, 2022; Cao *et al.*, 2024).

The application of epigenetic regulation in crop improvement is exemplified by the salt-tolerant rice cultivar *Pokkali*, where stress-responsive DNA methylation dynamics contribute to enhanced salinity tolerance and improved physiological performance under salt stress. Differential methylation patterns and flexible epigenetic responses in *Pokkali* highlight the potential of epigenetic mechanisms as targets for developing stress-resilient crop varieties (Karan *et al.*, 2015). Furthermore, activation of natural stress memory through eustressors and seed-priming technologies provides a cost-effective strategy for enhancing crop performance and transgenerational stress tolerance, making these approaches particularly attractive for sustainable agriculture and resource-limited farming systems

(Villagómez-Aranda *et al.*, 2022; Louis *et al.*, 2023). Their ability to dynamically regulate stress-related gene expression makes rRNA an attractive target for molecular breeding and epigenetic engineering aimed at developing climate-resilient and high-yielding crop varieties (Prasad *et al.*, 2025). Several studies in this direction have yielded insights into nuclear control of gene expression. Studies in *Triticum zhukovskyi* demonstrate that selective silencing and retention of specific nucleolar organizer regions (NORs) can influence chromosome behavior, particularly homologous chromosome pairing and meiotic stability. The loss of *T. urartu*-derived NORs and maintenance of *T. monococcum*-derived NORs facilitate genome stabilization by reducing unwanted interactions between homologous chromosomes during polyploidization (Huang *et al.*, 2023). Studies in *Brassica napus* have demonstrated that rRNA genes silenced in vegetative tissues are reactivated in all floral organs, including non-reproductive tissues such as sepals and petals. Thus, indicating the reactivation of under dominant rRNA genes is associated with floral development challenging the traditional hypothesis that nucleolar dominance is reversed only during gametogenesis (Song *et al.*, 2015). Polyploid crops are vital source of food and source of agronomical traits (Qin *et al.*, 2025). Since actively transcribed rDNA loci can function as chromosome pairing sites, manipulation of rDNA activity provides potential strategies for improving meiotic chromosome behavior in polyploid crops (McKee *et al.*, 2012; Schaart *et al.*, 2021). In synthetic hybrids, nucleolar dominance is gradually established over successive generations, and changes in parental genome dosage can reverse the direction of dominance emphasizing on nucleolar dominance and genome dosage rather than species-specific transcription factors (Xiao *et al.*, 2016). The study of nucleolar dominance in *Spartina* allopolyploids highlights its importance as a model for understanding genome stabilization and epigenetic regulation following interspecific hybridization. The rapid establishment of nucleolar dominance in first-generation hybrids and its maintenance after polyploidization demonstrate that selective rRNA gene silencing contributes to the stabilization of hybrid genomes during the early stages of allopolyploid evolution (Kudrova *et al.*, 2026). The observed maternal bias in rRNA gene expression further provides insights into parent-of-origin effects and subgenome interactions (Xu *et al.*, 2023). Harnessing non-additive, maternally biased gene regulation helps breeders predict and select superior biomass and yield traits in hybrid crosses. As demonstrated in yield and fibre traits in *Gossypium arboreum* (Sukurtha *et al.*, 2023). Also, utilizing maternal epigenetic states allows breeders to develop climate-smart seeds that retain adaptive transcription patterns for early abiotic stress resilience (Brunel-Muguet, *et al.*, 2025). The research finding that nucleolar dominance is regulated primarily by differential DNA methylation rather than rRNA gene dosage identifies epigenetic modification as a key target for manipulating rRNA gene expression. These observations have important applications in hybrid crop breeding, epigenetic breeding, and polyploid genome engineering by facilitating the development of stable, high-performing, and climate-resilient crop varieties through the modulation of epigenetic pathways controlling nucleolar dominance (Borowska-Zuchowska *et al.*, 2023; Borowska-Zuchowska *et al.*, 2017).

Epigenetic breeding has emerged as a promising approach for accelerating crop improvement by exploiting heritable epigenetic variation to enhance stress tolerance, productivity, and climate resilience without altering the underlying DNA sequence (Turcotte *et al.*, 2022; Cao *et al.*, 2024). Among the most practical applications is stress priming, in which exposure to mild environmental stress induces epigenetic modifications that establish stress memory, enabling plants and their progeny to respond more effectively to subsequent stress conditions (Liu *et al.*, 2022; Louis *et al.*, 2023). The advantage of Stress priming is that it preserves ribosomal RNA (rRNA) and DNA integrity during seed pre-treatment. This boosts metabolic readiness, protein synthesis, and cellular defense, enabling crops to tolerate drought, salinity, and heat (Liu *et al.*, 2022). Alterations in RNA biology are a common feature of cancer and play a critical role in tumor development and progression. RNA-mediated alterations influence multiple cancer-related pathways (Gregory *et al.*, 2021). The epigenetic regulation of rRNA genes by the nucleolar

remodeling complex (NoRC), particularly through TIP5 is essential to regulate ribosome biogenesis and cellular proliferation as demonstrated through animal models. Since NoRC-mediated silencing of rRNA genes suppresses ribosomal RNA transcription, reduces nucleolar size, inhibits cell proliferation, and shifts rDNA replication from early to late S phase. This establishes and maintaining a stable heterochromatic state at NOR (Srivastava *et al.*, 2016; Panov *et al.*, 2021). Consequently, modulation of the NoRC-TIP5 pathway represents a promising strategy for controlling abnormal nucleolar activity associated with cancer, where elevated rRNA synthesis and enlarged nucleoli are common hallmarks (Pietrzak *et al.*, 2020). The review by Quin *et al.*, 2016 describes the approaches and biology behind nuclear targeting in Cancer. In addition, manipulation of NoRC-dependent chromatin remodeling may facilitate epigenome engineering approaches aimed at regulating rDNA expression. Synthetic targeting of NoRC components (such as TIP5) to genomic sites allows long-term, heritable repression of aberrant or hyperactive genes in diseases (Dai *et al.*, 2024). The NoRC-TIP5 pathway facilitates genome integrity, and has improved our understanding of chromatin dynamics in development, aging, and regenerative medicine. During aging, the decline of protective factors like sirtuins impairs NoRC recruitment, leading to heterochromatin loss, nucleolar stress, and cellular senescence. In regenerative medicine chemical and physical relaxation methods reduce reliance on integrating viral vectors leading to downstream tumor risks. Hence NORC mediated remodelling has application in medicine. It has found application in relaxing the rigid heterochromatin to ease somatic-to-pluripotent transitions. Yoder *et al.*, 2025 report enhanced nuclear plasticity enables smoother *in vitro* expansion or direct *in vivo* tissue repair in injury-related diseases.

Growing evidence indicates that changes in nucleolar structure and activity are important hallmarks of aging. Aging is generally associated with altered ribosome biogenesis and changes in nucleolar organization which are regulated by nutrient-sensing pathways, epigenetic modifications, and nucleolar proteins (Corman *et al.*, 2023). Increased nucleolar size and enhanced ribosome biogenesis have been reported in premature aging disorders, aged human fibroblasts, and senescent cells. In model studies of yeast, *Caenorhabditis elegans*, *Drosophila*, and mice research implicate reduced nucleolar activity is consistently associated with lifespan extension. Notably, experimental reduction of nucleolar activity promotes longevity, while increased ribosome biogenesis abolishes lifespan extension in *C. elegans* (Tiku *et al.*, 2017). The results of the study opens prospects for regenerative medicine in several human aging diseases. The selective silencing independent of the parental origin of the genome and is mainly controlled by differences in transcriptional enhancers and species-specific transcription factors (Wolff *et al.*, 2025; Lewis *et al.*, 2021). Importantly, the repressed rRNA genes can be reactivated at later developmental stages, indicating that nucleolar dominance is a reversible epigenetic process (Warsinger-Pepe *et al.*, 2020). Because these chromatin and DNA methylation patterns can be turned on or off, studying this dosage-control switch offers fresh avenues for treating diseases like cancer and correcting transcriptional dysfunctions in diseases (Castro-Muñoz *et al.*, 2023). Neurons require exceptionally high levels of ribosome biogenesis to support their large size, extensive synaptic networks, and high metabolic activity. Consequently, nucleolar function and rRNA synthesis are critical for maintaining neuronal growth and function (Slomnicki *et al.*, 2016; Fee *et al.*, 2022). Alterations in nucleolar activity have been closely associated with several neurodegenerative disorders (Parlato *et al.*, 2013; Lourenco *et al.*, 2025). In Parkinson's diseases, reduced nucleolar size and impaired rRNA synthesis are linked to defective protein synthesis (Garcia-Esparcia *et al.*, 2015), whereas enlarged nucleoli have been reported in C9ORF72-associated Amyotrophic lateral sclerosis (ALS), indicating disease-specific alterations in nucleolar function (Arogundade *et al.*, 2021). Specific non-coding regions (rRNA) are involved in the replication of viruses (such as targeted endogenous transcripts) (Yamin *et al.*, 2025). Research evidences implicate that RNAi machinery can be successfully targeted to silence preventing the assembly of new viral particles within the nucleolus, thus enabling anti-viral therapy (Ulloa-Aguilar *et al.*, 2024).

DISCUSSION

Multicellular organisms' somatic cells are genetically similar, yet their nuclear architecture and gene expression patterns can vary greatly (König *et al.*, 2020). The expression of 45S rRNA genes acquired from one progenitor as a result of the other progenitor's rRNA genes being silenced is known as nucleolar dominance, an epigenetic process that happens in genetic hybrids (Kuderová *et al.*, 2026). The mechanisms underlying nucleolar dominance are still unclear today, despite a lengthy history of research and its occurrence in interspecific hybrids ranging from plants, invertebrates, frogs, flies, fish, and mammals. Noncoding RNAs are essential for selective rRNA gene inactivation in nucleolar dominance, a large-scale gene silencing event, according to recent findings (Warsinger-Pepe *et al.*, 2020). This system is crucial for regulating the amount of active rRNA genes in both plants and animals. It also enables chromatin-mediated silencing of one parental set of rRNA genes in genetic hybrids. The rRNA gene's on and off states are determined by identical cytosine methylation and histone modifications in plants and mammals, suggesting an ancient basis for the epigenetic regulatory system. Near the chromosomal region where tandemly repeated 35-48S rDNA is transcribed, a nucleolus forms (Borowska-Zuchowska *et al.*, 2023). The 18S, 5.8S, and 25-28S rRNA molecules that make up ribosomes and are necessary for cell viability are encoded by the 35-48S rRNA genes (Báez *et al.*, 2020). Understanding the significance of proper rRNA processing has been made possible by the developmental effects of altered rRNA processing in a number of plants. Numerous insights into the study of ND have been provided by cytological investigations. In addition to differentiating between active and inactive 35S rDNA loci, the use of silver staining in conjunction with the flagship cytomolecular technique of fluorescence in situ hybridisation (FISH) and its modification, genomic in situ hybridisation (GISH), also identifies the subgenome origin of specific loci in interphase nuclei (Pikaard *et al.*, 2023; Liu *et al.*, 2023). Studies of tandem repeats, including 35S rDNA, in both the sequence and DNA methylation settings have entered a new phase with the advent of long-read sequencing technologies with ultralong reads, such as nanopore sequencing and single-molecule real-time sequencing (Espinosa *et al.*, 2022). Higher-order organization of the NOR2 locus of *A. thaliana* has recently been evaluated using a combination of long- and short-read sequencing of bacterial artificial chromosomes containing rDNA (Sims *et al.*, 2021). In addition to revealing the variability of rDNA units, the study shed light on the tissue-specific patterns of their expression. Similarly, the reconstruction of individual rDNA loci in wheat has recently been made possible by integrating optical maps of flow-sorted chromosomes with short-read sequencing data (Tulpová *et al.*, 2022). Research on polyploids has provided valuable insights into the molecular and cytogenetic elements of nuclear dominance. One such element is the function of transcription factors (TFs) in nuclear dominance. According to research by Borowska-Zuchowska *et al.* (2023), transcription factors (TFs) that recognise the promoter and interact with Pol I coevolve with the rapid evolution of rRNA gene promoters. According to the findings, ND enforcement is caused by the absence of species-specific TFs in hybrid or allopolyploid individuals. In fact, this theory seems to hold true for uncrossable distantly related species. According to a different study by Long *et al.* (2015), distant hybridisation between *Brassica alboglabra* and *Raphanus sativus* causes nucleolar chromatin rearrangement and rDNA genetic imbalance. Cumulatively, according to these research chromosomal rearrangements, genetic imbalances, and epigenetic patterns may govern the expression of rRNA genes in intergeneric hybrids and control nucleolar structure and chromatin remodelling. It has long been unclear how to choose a single group of rRNA genes for inactivation. Since imprinting in the gametes does not seem to be engaged in developmental regulation after embryogenesis, several theories, such as maternal or paternal effects, have failed to explain nucleolar dominance. Unlike the spontaneous inactivation of one X chromosome in somatic cells of female eutherian mammals, nucleolar dominance is not a random event. Rather, the same set of parental rRNA genes is consistently silenced. Since NORs with less rRNA genes can be dominant over NORs with more rRNA genes, this selection mechanism is not only dependent on the quantity of rRNA

genes at a NOR. Additionally, nucleolar dominance cannot be explained by the theory that inactivating a species-specific transcription factor might inactivate the corresponding collection of rRNA genes. Because the rRNA genes of the progenitors in plant hybrids are fully functional when transfected into the other species. However, rather than co-ordinately down-regulating the rRNA genes inherited from both progenitors, it is still unknown how or why one paternal set of rRNA genes should be preferentially switched off. It is extremely improbable that ribosomes originating from either parent's rRNA genes will differ functionally because the coding sections of the rRNA genes are almost identical in organisms that are capable of interbreeding. In an effort to identify explanations, researchers have concentrated on the sequence variations in the rRNA genes themselves. Variations in the kind or amount of intergenic spacer repeats have been suggested to regulate nucleolar dominance in *Xenopus* and *Solanum* (Michalak *et al.*, 2015; Hemleben *et al.*, 2023).

The intergenic spacers of *X. laevis* and *X. borealis* differ in the quantity and kinds of repetitive sequences (Caudy *et al.*, 2002). Co-injected minigenes containing X are subordinated to promoters with nearby *X. laevis* spacer sequences cloned upstream. Similar to the direction of nucleolar dominance in *X. borealis* spacer sequences are connected to the promoter. X is *Laevis*. hybrids of the *borealis*. The dominance of *X. laevis* rRNA genes may therefore be explained by variations in the binding affinities of one or more limiting transcription factors to the enhancers (Paule *et al.*, 2000). Research has shown that the spacer promoter repeats are arranged in order for X upstream of the enhancer. In injected oocytes, laevis spacers confer dominance, indicating that transcription of the spacer repeats is required to activate the downstream gene promoter (De Winter *et al.*, 1986). Transient expression or *in vitro* transcription investigations in plants do not support the appealing theory that dominant genes have a larger binding affinity for one or more transcription factors (Chen *et al.*, 1998). Further, research utilising massive doses of rRNA minigenes injected into *Xenopus* oocytes also provide similar evidences (Taylor *et al.*, 1985). Since recombination is inhibited on chromosome arms near NORs in plants and other eukaryotes (Stack *et al.*, 2017), it is worthwhile to take into account the possibility that a NOR locus regulatory area may be connected to the observed rRNA gene sequence polymorphisms. Another observation is that nucleolar dominance is the outcome of controls applied to NORs as the regulatory units rather than at the level of individual rRNA genes. Genetic research on inter-ecotype hybrids of *Arabidopsis thaliana* provides evidence for this mechanism (Moore *et al.*, 2011). The idea that nucleolar dominance provides specificity, is influenced by RNA base-pairing interactions is supported by more recent research findings (Lu *et al.*, 2018). Nucleolar dominance is characterised by the up-regulation of the dominant set of rRNA genes and the concurrent repression of the underdominant set of genes, as experiments with wheat-rye hybrids have shown (Neves *et al.*, 1995). Evidence suggests that intergenic pRNA transcripts can cause rRNA genes to be silenced in trans in mice (Calero-Nieto *et al.*, 2010). Additionally, proteins of the RNA-directed DNA methylation pathway that use siRNAs that can operate in trans at homologous loci are known to be involved in nucleolar dominance (Burgess *et al.*, 2022). Therefore, it seems possible that the repressed class of rRNA genes is silenced as a result of transcription of the dominant class. The experiment in which *Arabidopsis thaliana* × *A. lyrata* hybrids, rRNA transgenes integrated at ectopic loci escape the silencing imposed on rRNA genes within the *A. thaliana* NORs, provides additional scientific evidence that the NOR, rather than individual rRNA genes, may be the unit of regulation in nucleolar dominance (Lewis *et al.*, 2007). The roles of NORs and rRNA genes have been the subject of extensive cytological and molecular research. Investigating and identifying other dosage control system components would be future objectives for further research in this field. Also, determining how the different chromatin-modifying processes interact to pair changes in DNA methylation and histone modification is another avenue. It is still an enigma how complete NORs or subsets of rRNA genes are chosen for inactivation. Finally, additional consideration and experimental research are required to establish the regulation that takes place at the level of entire NORs rather than one rRNA gene at a time. Comprehending these mechanisms will

undoubtedly provide fresh insight into the initial establishment of nucleolar dominance and provide more insights into how rRNA gene dosage levels are set, maintained, and/or readjusted across numerous cell cycles in non-hybrids. Understanding how environmental cues are converted into quantitative changes in ribosome output in the field of plant biology will depend on finding upstream signals, sensors, and regulatory elements that impact the processing machinery. Next, the relationship between rRNA surveillance pathways and rDNA variant usage represents another aim for future investigations.

CONCLUSION

Nucleolar dominance is a special epigenetic mechanism that causes ribosomal RNA (rRNA) genes inherited from one parent to be preferentially expressed while those from the other parent are transcriptionally repressed. This process is regulated by chromatin modifications, DNA methylation, histone modifications, chromatin-remodeling complexes, and non-coding RNAs that alter the accessibility of rRNA gene loci. These systems enable normal cellular activity and genomic stability in addition to preserving nucleolar architecture and guaranteeing appropriate rRNA synthesis. Research over the last few decades has demonstrated that rRNA gene silencing is a dynamic and reversible process rather than a permanent genetic modification. Small RNAs and long non-coding RNAs play important roles in establishing or maintaining the quiet chromatin state by guiding chromatin-modifying proteins to specific rDNA sites. With a focus on the molecular mechanisms of RNA-directed DNA methylation, chromatin remodeling, nucleolar dominance, developmental regulation, environmental responses, and their applications in plant biology and agricultural biotechnology, this review summarizes our current understanding of RNA- and chromatin-dependent rRNA gene silencing in plants and mammals. There are many biological implications to comprehending RNA- and chromatin-dependent rRNA gene silencing.

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