The Dynamic Interplay Between Ribosomal DNA and Transposable Elements: A Perspective From Genomics and Cytogenetics

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Abstract

Although both are salient features of genomes, at first glance ribosomal DNAs and transposable elements are genetic elements with not much in common: whereas ribosomal DNAs are mainly viewed as housekeeping genes that uphold all prime genome functions, transposable elements are generally portrayed as selfish and disruptive. These opposing characteristics are also mirrored in other attributes: organization in tandem (ribosomal DNAs) versus organization in a dispersed manner (transposable elements); evolution in a concerted manner (ribosomal DNAs) versus evolution by diversification (transposable elements); and activity that prolongs genomic stability (ribosomal DNAs) versus activity that shortens it (transposable elements). Re-visiting relevant instances in which ribosomal DNA–transposable element interactions have been reported, we note that both repeat types share at least four structural and functional hallmarks: (1) they are repetitive DNAs that shape genomes in evolutionary timescales, (2) they exchange structural motifs and can enter co-evolution processes, (3) they are tightly controlled genomic stress sensors playing key roles in senescence/aging, and (4) they share common epigenetic marks such as DNA methylation and histone modification. Here, we give an overview of the structural, functional, and evolutionary characteristics of both ribosomal DNAs and transposable elements, discuss their roles and interactions, and highlight trends and future directions as we move forward in understanding ribosomal DNA–transposable element associations.

Key words: **repetitive DNA, ribosomal DNA, transposable elements, concerted evolution, homogenization, transposition, recombination, housekeeping genes, genome stability, genome size, molecular cytogenetics, long-read sequencing.**

Ribosomal DNAs and Transposable Elements: Two Opposing Faces of Repetitive DNAs

Ribosomal DNAs: Conserved and Heavily Transcribed, These Housekeepers Are In Charge of Cell Maintenance

Ribosomal RNA genes (rDNAs) play fundamental key roles in cellular processes. They are repetitive and encode the RNA components of ribosomes, the most ancient and complex of all molecular machines (Moss et al. 2006). Despite rDNAs not representing a large proportion of an organism's genome size, they produce around 80–90% of the RNAs found in most cells (Eaves et al. 2020) and ribosomal RNAs (rRNAs) accounting for 60% of the ribosomal mass (O'Connor and Adams 2010). Ribosomal DNA repeats are crucial players in maintaining genome stability (Kobayashi 2006) and any disturbance at rDNA loci may have a great impact on cellular processes, including the response to DNA damage and overall cell longevity (Ganley and Kobayashi 2014). Because of their universality, sequence conservation, and usually high copy numbers, rDNAs and their spacers have been widely used to resolve evolutionary relationships among organisms (Nieto-Feliner and Rosselló 2007) and deployed as molecular markers for breeding purposes or addressing hybridization processes (Garcia et al. 2020, 2023). Although highly conserved due to their housekeeping nature, there are some

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differences between prokaryotic and eukaryotic rRNAs (Fig. 1). Whereas prokaryotic ribosomes contain three rRNAs, the 16S, 23S, and 5S rRNAs, eukaryotic ribosomes carry four: the corresponding 18S, 26S (or 28S, depending on the organism group), the 5S rRNAs, and additionally, the eukaryote-specific 5.8S rRNA. Prokaryotes typically encode all rRNAs in a single operon, an arrangement thought to facilitate gene regulation. Nevertheless, in some bacteria and archaea, the 16S and 23S rRNA genes can occur in an unlinked manner (Brewer et al. 2020). In eukaryotes, 18S, 5.8S, and 26S/28S rRNA genes are usually encoded in a single operon, called 35S in plants and 45S in animals (Hemleben and Zentgraf 1994; Hemleben et al. 2021). Although it is generally assumed that the 18S–5.8S–26/28S operon spreads as a whole (Bueno et al. 2013), independent mobility of each of these genes has been occasionally observed, e.g. in fish (Symonová et al. 2013) and in grasshoppers (Ferretti et al. 2019). The fourth gene, the 5S rRNA, is the only one ubiquitous to prokaryotes and eukaryotes; it can be either linked (Garcia et al. 2009) to the other rRNA genes or separated from these, located in other genomic regions. Much less frequently, the 5S rRNA gene can also be linked to other multigene families, such as histone genes or the trans-spliced leader, or even, very occasionally, can be dispersed across the genome (Drouin and de Sá 1995).

Another distinction between prokaryotic and eukaryotic rDNAs is their copy number, ranging from a few operons in *Escherichia coli* (e.g. seven in strain K12) (Maeda et al. 2015) to hundreds to thousands of copies in plants and animals (Ingle et al. 1975; Prokopowich et al. 2003). Moreover, rDNA copy number is dynamic and can experience large interspecific and even intraspecific variation. Variation that can also be driven by environmental changes (Gibbons et al. 2014; Lavirinenko et al. 2021). Copy number of each of the rDNAs may be influenced by the need to maintain a balanced amount of 5S and 45S arrays. In this regard, Gibbons et al. (2015) demonstrated that 5S and 45S rDNA arrays of human and mouse exhibit a tightly coupled variation in copy numbers (a concerted copy number variation, cCNV), despite their location in different chromosomes. Although the exact mechanism(s) on how cCNV of rRNA genes is coordinated is unclear, the discovery of cCNV appears as a new way to achieve gene and genome balance (Malone 2015). Besides, rRNA transcription is also precisely regulated, as demonstrated by Condon et al. (1993) in *E. coli*, where a depletion of the number of functional rDNA copies lead to an increased expression of the remaining ones.

As other tandemly arranged multigene families, rDNAs generally evolve in concert. Concerted evolution is one of the molecular evolution models put forward for multigene families that keeps sequence integrity across all gene copies (Brown et al. 1972). Other options have been proposed to explain the evolution of rDNAs in certain cases such as the birth-and-death model (e.g. Pinhal et al. 2011; Zhang et al. 2021). In this model, gene variants arise by gene duplication with some staying for a long time in the genome whereas others become pseudogenized and ultimately deleted (Nei and Hughes 1992; Nei and Rooney 2005). Nevertheless, diversity in non-transcribed spacer (NTS) regions of rDNAs within and between species is common (Coen et al. 1982; Williams et al. 1990). Also, in the rRNA genes, intragenomic diversity has been found in species as distant as yeast (Sultanov and Hochwagen 2022) and human (Fan et al. 2022). Despite this, the concerted model explains the evolution of rRNA genes better than all other models proposed so far. A recent review, which addresses the intragenomic rDNA variation across a wide range of organisms, highlights that rDNA evolution is complex and still a subject of debate, even more than 50 years after the concerted evolution model for multigene families evolution was first proposed (Wang et al. 2023).

The rDNAs represent heavily transcribed units along the chromosomes. These actively transcribed 35S/45S rDNA loci constitute the nucleolus organizer regions (NORs), the site where ribosome biogenesis takes place. The nucleolus is the most visible component of the interphase nucleus, and its physical relationship with the rDNA locus was first recognized by Barbara McClintock in maize (1934). But the rDNA's presumed stability in chromosomal locations is untrue in some cases: already 40 years ago, mobile NORs were observed in *Allium* species (Schubert 1984; Schubert and Wolbus 1985). The mobile NOR hypothesis is based on the variable sizes, numbers, or chromosomal positions of rDNA loci after silver staining and in situ hybridization of rRNA genes. Over the last years, this observation was also shown for other taxa (e.g. Pedrosa-Harand et al. 2006; Schmidt et al. 2019). Mobility of rDNAs is a sporadic event and likely results from recombination rather than being a transposable element (TE)-mediated process. Yet, in the context of this review, it is interesting to note that rDNAs can sometimes be mobile.

Despite the long history of research into rDNAs, they still remain elusive (Hall et al. 2022). Due to their repetitiveness, they are usually absent from most of todays genome assemblies, and, despite the rDNA's significance for cellular maintenance, we still know relatively little about rDNA evolution, copy number preservation, and impact on genome integrity.

TEs: Hyperdiverse and Mostly Repressed, These Evolutionary Drivers Bring Genomic Novelty

In sharp contrast with rDNAs, TEs are dispersed genomic repeats, often termed "mobile DNAs" or "jumping genes". These sequences can change their position in the genome or generate copies of themselves in a process termed (retro-) transposition. Depending on the presence of an mRNA intermediate, TEs are classified as Class I - retrotransposons and Class II - DNA transposons (Finnegan 1989; Wells and Feschotte 2020). As such, TEs are the embodiment of the mobile genome and serve as agents of fast genomic change.

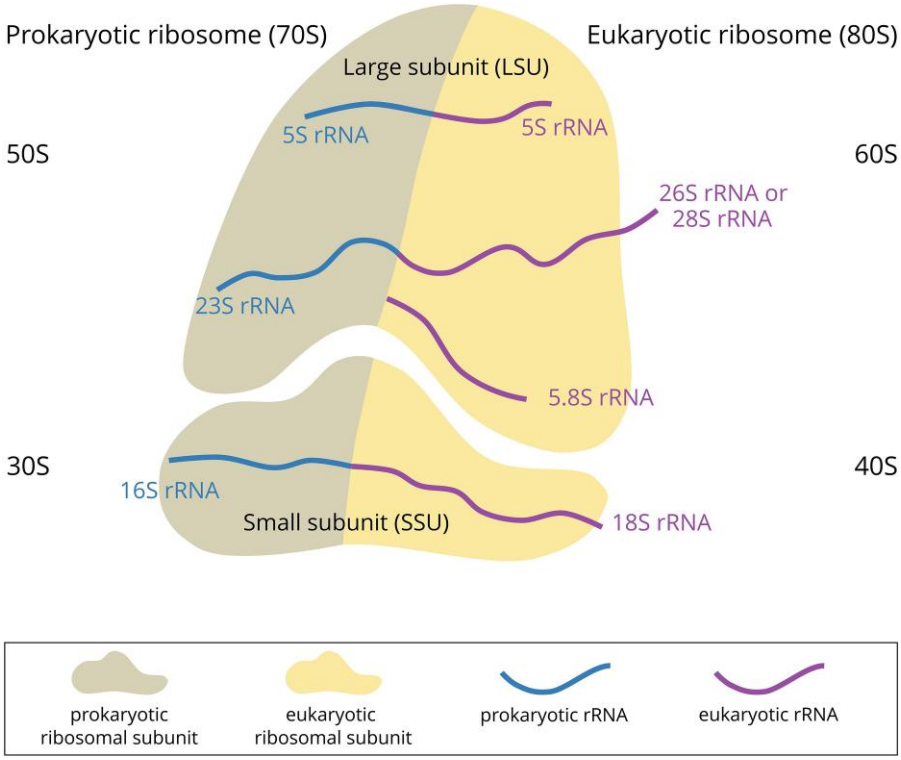


Fig. 1. Structure of a prokaryotic (left) and a eukaryotic (right) ribosome. The different rRNA components of both ribosome types are highlighted, focusing on prokaryotic (blue, left side of the ribosome), as well as the eukaryotic (violet, right side of the ribosome) variants. For the 26S/28S rDNA, the 26S variant is found in plants and the 28S variant in animals. The indicated rRNAs are encoded in the tandemly arranged rRNA genes.

TEs are ubiquitous. They have been detected across eukaryotes and prokaryotes including animals, plants, fungi, and bacteria. Unlike rRNA genes, making up only a tiny fraction of the genomes, TEs can account for up to 80–90% in some cases (Schnable et al. 2009) and they exist in a huge diversity, coming in many sizes, shapes, and proportions. Among TEs, long and short interspersed nuclear elements (LINEs and SINEs) are, by far, the most abundant in mammalian genomes (Platt et al. 2018), whereas long terminal repeat (LTR) retrotransposons dominate plant genomes (Gao et al. 2016).

Regarding the position of TEs in eukaryotic genomes, TEs are considered to be dispersed along the chromosomes. Despite this generalist view, there are many instances of TEs with non-random distribution: for example, *Arabidopsis thaliana* centromeres are enriched in certain Athila retrotransposons (Naish et al. 2021) and fruit fly telomeres are made up of HeT-A and TART (telomere-associated) retrotransposons (Silva-Sousa et al. 2012). It is now widely accepted that the observed patterns result from the interplay of TE insertion and TE removal mechanisms. To understand these complex TE integration dynamics, many TE mutagenesis and comparative genomics studies have been performed in the recent years (reviewed, for example, in Sultana et al. 2017).

Historically, it took not only the discovery of TEs in maize, by McClintock (1950), but additional years to accept that genomes "were not static, stable, and immobile" (as later highlighted by Kazazian 2011). Even then, TEs were mainly recognized as "junk" or "parasitic DNAs" contaminating the genome (Orgel and Crick 1980). In our current times, the perceived relevance and impact of TEs are again shifting. There is a growing conviction that TE disruption could indeed serve as evolutionary driver. Thus, TEs provide a reservoir of genetic and epigenetic variability, with some TEs even having adaptive potential (Chuong et al. 2017; Schrader and Schmitz 2019; Almeida et al. 2022). Despite the vast majority of studied TEs being deleterious, the advance of genomics brings forward more cases in which TEs take over new, unsuspected, and sometimes beneficial roles, such as gene master regulators, evolutionary drivers, and structural genomic components, among others.

In terms of molecular evolution, TEs also differ significantly from rDNAs. Since they are mostly free of selection pressures, they are hyperdiverse, and their mode of evolution is usually explained by the neutral theory (Kimura 1968; Arkhipova 2018). With neutrality, it is usually understood that insertional TE mutagenesis is mostly neutral or slightly deleterious (Arkhipova 2018). Of course, with the advance of genetics and genomics, more cases come to light where TE insertions cause disruption, but sometimes also produce phenotypic and/or regulatory variability. Two of the most well-known examples are Mendel's wrinkled peas and the industrial melanism of peppered moths (Bhattacharyya et al. 1990; van't Hof et al. 2016). Regarding TE evolution within the host, we outline the typical life cycle of a TE according to the birth-and-death model, the currently favored model explaining TE evolution in the host (Blumenstiel 2019):

1) *Birth and initial amplification*: typically, point mutations or modular reshuffling can lead to enough sequence variation that a TE arises, which is not yet

silenced by the epigenetic machinery, but still contains all necessary components for activation. This is usually followed by an initial amplification ("burst of amplification") that increases the copy number of the new variant. Along these lines, a TE family is typically considered active or mobilizable, if its members (at least one member) are capable of producing TE copies under favorable circumstances. Depending on the TE type, this often involves harboring continuous, undisrupted open reading frames and intact promoters. The hallmarks of an active TE family are much more difficult to define, if non-autonomous TE families are concerned, which often do not encode any protein domains.

2) *Silencing*: After amplification, the host's epigenetic silencing machinery will silence the TEs. Depending on the genomic circumstances, re-activation is possible, if silencing was released.
3) *Decay and death*: Over evolutionary timescales, by accumulation of mutations, the TE's potential to be mobilized will decrease, until the TE is either decayed or deleted, e.g. by recombination (Devos et al. 2002). Of course, the process of mutation can also lead to the emergence of new TE variants, thus starting anew the TE life cycle.

rDNA and TEs: Bridging the Differences and Coming Together?

Summarizing, while rDNAs make up a small but essential genomic fraction, TEs make up the largest but mostly dispensable part of the genome, but are essentially disregarded in their functions; while the rDNA's organization is in tandem, localized in specific chromosomal loci, TEs are typically dispersed across genomes; while at least some rDNA loci are always active, TEs are silenced in their majority; while rDNAs tend to homogenize their sequences, diversification is the rule for TEs; and while rDNAs follow preferentially a concerted mode of evolution (Wang et al. 2023), the evolution of TEs may better fit the birth-and-death model.

Yet, both rDNA and TEs also have several things in common: (1) while TEs and their derivatives are certainly major contributors to genome size, recent evidence suggests that rDNA by-products (such as pseudogenized rDNA copies and/or fragments) can also contribute to the "junk DNA" accumulating over evolutionary time (Robicheau et al. 2017). (2) In terms of mobility and chromosomal positioning, TEs occasionally jump into ribosomal DNA loci and can integrate more-or-less stably in some rDNA arrays; upon re-activation, TEs may carry rDNA fragments (Pérez-González and Eickbush 2001) and distribute them across the genome in their path (see "Ribosomal DNA in TEs" of this review). Hence, TEs have the potential to structurally embed rDNA sequence units, to mobilize rDNA copies, and to diffuse the rDNA's restriction to distinct chromosomal sites (although such processes may also be explained by recombination). (3) Regarding activity, TE-mediated silencing can sometimes spread to silence rDNA chromatin. Hence, some TE insertions have been shown to prevent rDNA transcription (Long and Dawid 1979; Jamrich and Miller 1984; Fefelova et al. 2022). Interestingly, if TEs are transcriptionally activated, rDNA can follow (Fefelova et al. 2022). Similarly, TEs embedded in the rDNA or using rDNA promoters (see "TEs in Ribosomal DNA" and "Ribosomal DNA in TEs" of this review) may circumvent silencing and be actively transcribed.

Evolutionarily speaking, the mechanistic differences between rDNA and TEs are sometimes overridden: occasionally, similarly to TEs, rDNA copies emerge and decay according to the birth-and-death model (see above). Complimentarily, in a few instances, TEs may also evolve by homogenization, reminiscent of rDNAs: first, they may act as entry points for illegitimate recombination processes, leading to copy number expansion or contraction (Devos et al. 2002). Second, TEs may also be homogenized across the genome by non-allelic gene conversion events, thereby spreading mutations from one copy to another (Kejnovsky et al. 2007; Ellison and Bachtrog 2015; Fawcett and Innan 2019). Third, occasionally, TEs can form tandemly repeated structures undergoing homogenization (Paço et al. 2019; Maiwald et al. 2021). Nevertheless, TE-driven homogenization is usually not considered a dominant force: instead, recent large sequencing works show TEs as the titular antagonists that disrupt ongoing homogenization processes (Naish et al. 2021).

Here, we address the complex relationship between rDNAs and TEs (Fig. 2), two of the most salient figures of genomes, by analyzing the evolution of methodological approaches to reveal rDNAs, TEs, and their interactions and also by reviewing relevant instances in which an interaction between both has been described. We also aim to find connections between both, aiming to understand how their interactions may contribute to their mutual evolution and genomic distribution and how this can provide material for genomic innovation. We finally address their molecular evolution, mobility, and trajectory across the cellular lifespan in these interactions, given that both rDNAs and TEs play major roles in genome evolution, chromosomal stability, and gene regulation.

Methods to Detect rDNA, TEs, and Their Associations

Method-wise, due to their repetitiveness, the most striking rDNA and TE similarity is their absence from genome assemblies. TEs and rDNAs usually clutter up the "chromosome 0" or "random chromosome", where the unassembled bits and pieces are compiled. Nevertheless, during the past 50 yr, many methods were brought forward that have the potential to identify rDNA–TE associations.

In the 1970s, reannealing kinetics studies by Flavell et al. (1974) already established a clear relationship between genome size and the proportion of repetitive DNAs—a positive and usually significant correlation. In other words, most genome size variation is due to the variation in

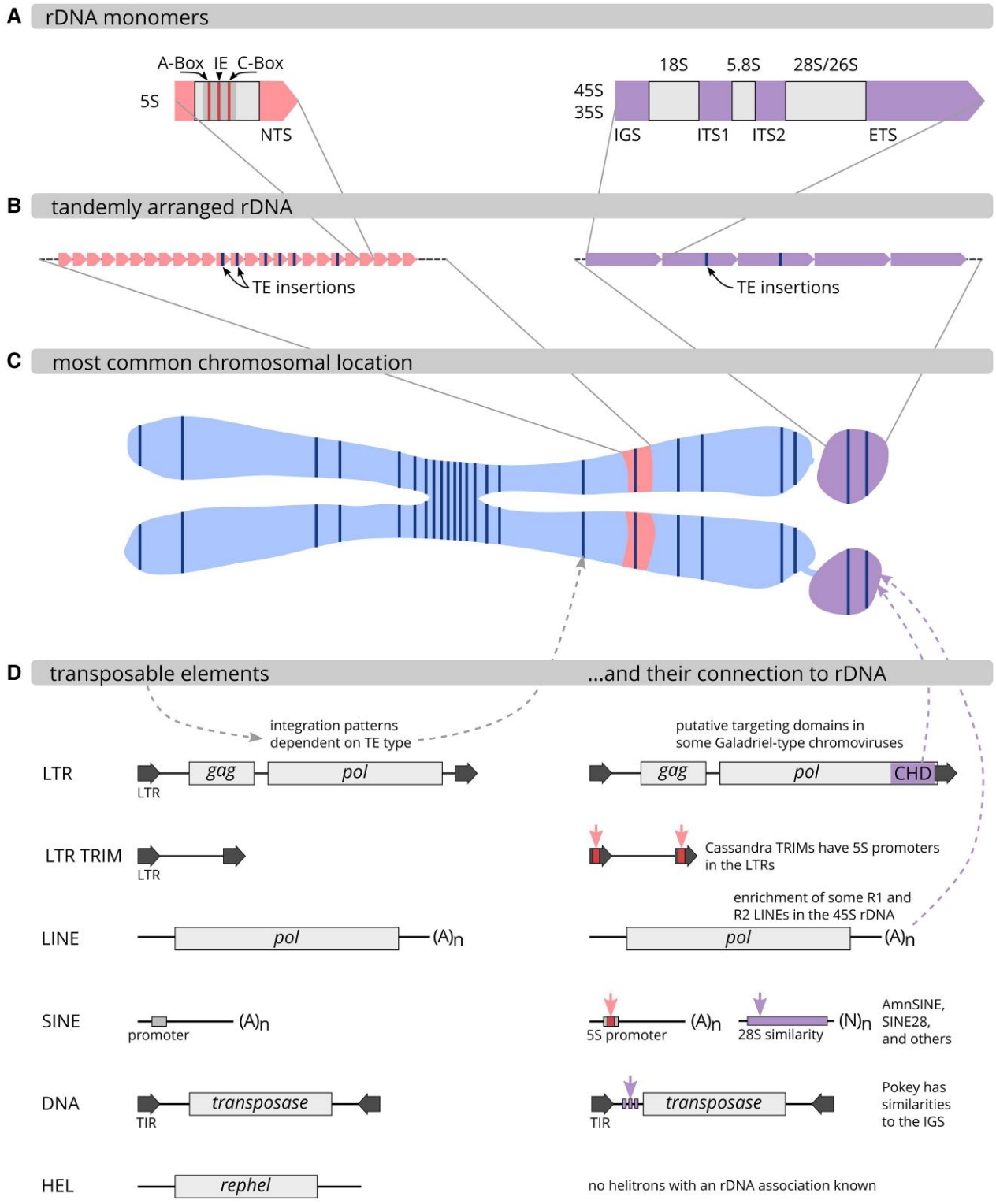


Fig. 2. Association of rDNAs with TEs. A) rDNA unit (monomer) composition follows a strict blueprint as they always contain the genetic information for the actual ribosomal genes (highlighted in gray), which are separated by spacer regions (left, red: 5S rDNA, right, purple: 35S/45S rDNA). Spacers are named according to their positions. As the 5S rDNA spacer is usually not transcribed, it is called NTS. The 35S/45S rDNA monomer is composed of the 5′ ETS, a several kb-long coding region, a 3′ ETS, and an IGS. The spacing units in between coding regions are called ITS. For 5S rDNA, we also observe an internal control region, with highly conserved promoter box motifs (A-Box, intermediate element, and C-Box) for Polymerase III transcription. The 35S/45S monomer consists of multiple rDNA genes for 18S, 5.8S, and 26S/28S rDNA. B) rDNA monomers appear in large numbers and form large arrays with a tandem arrangement. Insertions of TEs are highlighted in blue. C) Usually, the 35S/45S rDNA resides distally on the chromosomes, whereas the 5S rDNA occupies interstitial chromosomal loci. D) Some TEs are associated with these rDNA sequences and/or locations. This has been described for various types of TEs, such as the LTR retrotransposon lineage Galadriel and the LINEs R1 and R2 that target the 26S/28S rDNA; as well as many non-autonomous TEs (including SINEs, Cassandra TRIMs, and DNA transposons) that harbor rDNA-derived sequences such as the 5S promoter.

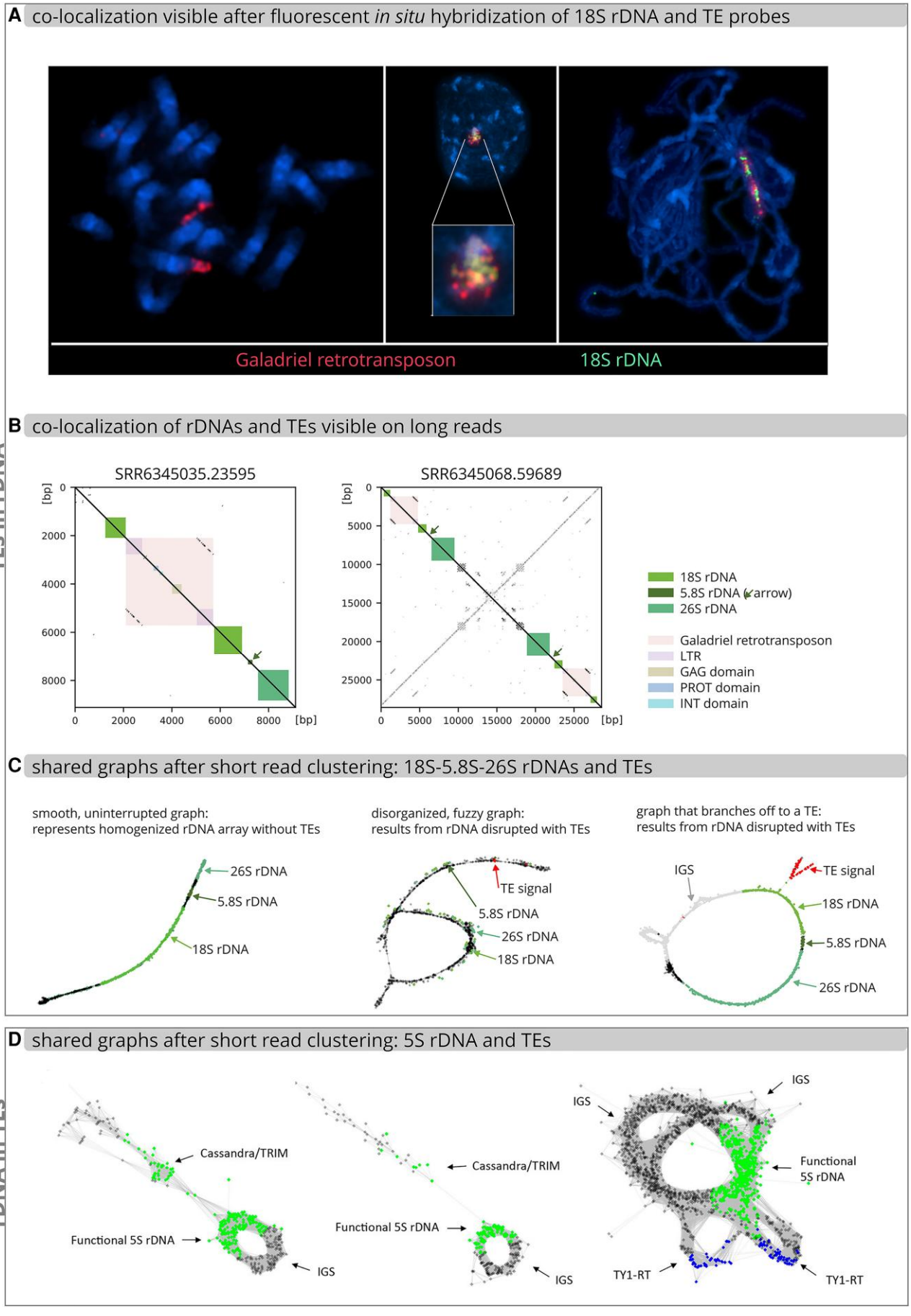
repeated DNA. This still holds true today, with caveats being polyploidy-related genome growth and the accumulation of sequence remnants of formerly repetitive DNAs in mega-genomes (Novák et al. 2020). The rise of molecular biology methods in the 1980s led to the identification of the most abundant repeats by Southern blot hybridization of genomic DNA with radioactively labeled probes, usually with short exposition times. The first cloning and sequencing experiments revealed all kinds of repeats, among them were ribosomal DNAs and fragments of the most abundant TEs. Already in the late 1970s, the presence of insertion sequences (a kind of short, simple TE) in ribosomal DNA was detected by Northern blot hybridization in *E. coli* (Nisen and Shapiro 1979). Insertions into many rDNA monomers of *Bombyx mori*, detected by restriction analysis (Lecanidou et al. 1984), were later identified as R1/R2 elements (Xiong and Eickbush 1988). Likewise, PCR, Southern blot, and similarity searches suggested that proximal rDNA-flanking sequences may consist of retrotransposons in rice (Fujisawa et al. 2006).

Cytological methods have also been a classical tool to show rDNA and TE (co)localization along chromosomes, usually focusing on TE integrations in rDNA (see "Ribosomal DNA in TEs" of this review). One of the first techniques to be developed was silver staining of interphase nuclei and chromosomes: silver nitrate reacts strongly with proteins and allows for visualization of actively transcribed rDNA loci (Bloom and Goodpasture 1976; Blum et al. 1987); however, a real surge in understanding arose when molecular methods were more regularly combined with cytology in the 1990s. This coincided with the spread of cytogenetic and fluorescent in situ hybridization (FISH) techniques. Due to the universal conservation of the ribosomal genes, rDNAs were not only among the first repetitive sequences to be identified for most organisms but also the first repeat probes to be hybridized. As even rDNAs from distantly related organisms can be used as FISH probes for many species, they are still among the most used probes for karyotyping (Heitkam and Garcia 2023). More than 2,000 papers have been published reporting the number and position of rDNA loci in chromosomes of plants and animals, and this information has been organized and summarized in www.plantrdnadatabase.com (version 4.0 February 2023; Rodríguez-González et al. 2023) and in www.animalrdnadatabase.com (Sochorová et al. 2018), respectively. TEs, however, are far more diverse and require identification and characterization experiments prior to cytogenetic use. Hence, their adoption for cytogenetics has been lagging. In most experiments, TEs were mapped dispersedly along the chromosomes, with some notable exceptions: for example, TEs of the Chromovirus lineage frequently reside in specific chromosomal positions: CRM-*type* chromoviruses are often centromeric (Neumann et al. 2011; Weber et al. 2013), whereas Galadriel-*type* chromoviruses are often detected within 35S rDNA copies (Balint-Kurti et al. 2000; Weber et al. 2013). These kinds of rDNA–TE associations can be visualized using two-colour FISH onto mitotic, meiotic, and interphase nuclei as well as onto stretched DNA fibers (Fig. 3A; also see "TEs in Ribosomal DNA" for further biological details on this specific rDNA–TE association).

The genomics era brought a new dimension to our understanding of the associations between rDNA and TEs. Conserved and tandemly arranged genes such as rDNAs are straightforward to identify along newly generated sequence data. In contrast, the high diversity of TEs complicates their identification and requires a range of diverse, often not integrated, tools (TE Hub Consortium et al. 2021). Due to the collapsing of repetitive regions in genome assemblies, most insights are gained from assembly-free approaches, using both short and long reads. The high sequencing throughput coupled with fast software development have now revealed rDNA and TE features and their possible interactions, which only a few years ago would have been difficult to imagine. Long reads are especially ideal to gain insights into the fine organization of rDNA and TEs, including their genomic environments. Automatized dot plotting tools like Flexidot (Seibt et al. 2018) allow the visualization of their respective positions. For example, self-dotplots of the Galadriel-type chromovirus mentioned above reveal the embedment into the 18S gene of the rDNA of sugar beet (Fig. 3B). Other tools, such as the computational pipeline RepeatExplorer (Novak et al. 2010, 2020), allow to identify and characterize repetitive DNAs in next-generation sequencing data, using graph-based clustering of sequence reads to identify repetitive elements. The resulting repeat clusters portray, for example, the homogenization of the 35S rDNA locus by smooth, uninterrupted 18S–5.8S–26S rDNA graphs (Fig. 3C, left), and may also show TE-disrupted loci as fuzzy or branched graphs (Fig. 3C, middle and right). Sequence similarities between rDNA and TEs (see "Future Perspectives" of this review) can also be revealed, as for example by shared graphs between the 5S rDNA and the 5S promoter-containing Cassandra TEs (Fig. 3D; Garcia et al. 2020). For the future, as genomics becomes more accessible for research on all organisms, we predict that more sequence-based methods to resolve rDNA–TE associations will be developed. Nevertheless, due to the repetitive nature of both, we recommend corroboration by molecular biology and/or cytogenetics to exclude being misled by sequence artifacts.

TEs in Ribosomal DNA

Many studies have reported the presence of TEs or TE fragments within rRNA genes, in their spacers or their close vicinity; a summary of the most relevant cases in animals, plants, fungi, protozoans, and bacteria can be consulted in Table 1. While in the earlier works the precise localization of TEs was not possible, with cytogenetic and genomic technological advances newer studies exactly positioned these TEs in the rDNA. Some TEs occur exclusively within rDNA arrays, whereas others are more widespread and dispersed with only some copies in the rDNA. The latter seems to be more prominent and here we lay out some plant-



specific specific examples: in sugar beet, some TEs such as the LINE BNR1 (Heitkam and Schmidt 2009) and the endogenous pararetrovirus beetEPRV3 (Schmidt et al. 2021) have some copies in the rDNA, but many more in other genomic regions. This observation is not limited to beets, but represents a general phenomenon (e.g. Raskina et al. 2008). In contrast, specific TEs targeting or accumulating in the rDNA have also been detected, such as Ty3-*gypsy* LTR retrotransposons of the Galadriel clade; one example is the Monkey element, found in the banana genome (Balint-Kurti et al. 2000; Hríbova et al. 2010), which has been recently confirmed on long reads (Eva Hríbova, personal communication). Galadriel-type TEs were also found in some of the 18S genes in sugar beet and other *Beta* species (Fig. 3A–C; Weber et al. 2013). Nevertheless, the sugar beet genome contains about 1,200 potentially functional 18S rDNA copies lacking TE insertions (Fig. 3C). Similarly, full-length Galadriel elements have been found integrated into the 18S gene in tomato [also called tomato rDNA-related retrotransposons (TRRTs); Jo et al. 2009], which was later sorted into the Galadriel lineage (Weber et al. 2013). This observation was later repeated in the mango genome, suggesting that this could be a common phenomenon (Nusrat Sultana and Tony Heitkam, personal communication). The chromodomains in the Galadriel lineage likely allow targeting of the open chromatin, of the rDNA, to allow integration of Galadriel-type TEs (Novikova 2009; Weber et al. 2013).

In animals, there are many examples of TEs in the 28S rDNA: especially the piggyBac-type DNA transposon Pokey has colonized the rDNA of several *Daphnia* species (Penton et al. 2002; Penton and Crease 2004; Glass et al. 2008; Eagle and Crease 2012; Elliott et al. 2013). There are also several reports of R1, R2, and R4 elements, classified as LINEs, integrating into the 28S rDNA. These LINEs are nearly ubiquitous in arthropods, such as *Drosophila melanogaster* (Jakubczak et al. 1992; Luo et al. 2020), *B. mori* (Xiong and Eickbush 1988), some parasitoid wasps and honeybees (Bigot et al. 1992), and also in beetles (Eickbush et al. 2013), reptiles, echinoderms, arachnids, crustaceans, and fish, among others (Kojima and Fujiwara 2005); see Table 1 for more examples. Insertions of these R elements often occur in non-essential regions of the 28S gene, thus favoring the conservation of insertion sites (Kojima and Fujiwara 2005). Eickbush et al. (2013) hypothesized that R2 elements lacked their own promoters, relying on the rDNA transcription machinery for their expression. Considering that rDNA arrays are prone to copy number loss due to their repetitiveness, Nelson et al. (2023) recently proposed the challenging idea that R2 would indeed be essential for maintaining rDNA copy numbers (see "Future Perspectives"), defying the notion that retrotransposons are solely self-serving elements.

As for the intergenic spacer (IGS) of the 35S/45S rDNA, there are also several works reporting TE integration; indeed, the IGS is highly variable and repetitive, and hence, prone to TE insertion polymorphisms. Among the most relevant TEs integrating in the IGS, we highlight the Alu SINEs, found in primates, including humans (González et al. 1993), and the LTR retrotransposon Hideaway detected in the fungus *Ascobolus immersus* (Kempken 2001). In *Nosema bombycis*, members of four miniature inverted-repeat transposable element (MITE) families were detected in the genic and intergenic rDNA regions, with the rDNA remaining fully functional (Liu et al. 2013). In some lepidopterans (here: *Inachis io*), the recent work by Daliková et al. (2023) reported the association of the IGS with an R2 element and a satellite DNA. Also, in the same organism group (here: *Hepialus humuli*), a non-functional Ty3/gypsy retrotransposon was detected at the very end of the rDNA unit [at the junction between the 28S rDNA and the external transcribed spacer (ETS)]. The authors concluded that mobile elements would have hardly contributed to mediating the spread of rDNA, while conversely, the satellite DNA arrays found in the IGS could have promoted the homology-mediated spread of rDNA through ectopic recombination or by integrating

Fig. 3. Methods to identify rDNA–TE associations. A) Using cytogenetics, an association of rDNAs and TEs becomes visible by co-localization of the respective signals. In this example, sequences corresponding to the Galadriel-type retrotransposon (red) and the 18S rDNA (green) are hybridized to sugar beet nuclei. Along the mitotic metaphase chromosomes, hybridization of Galadriel clearly shows two major sites covering the typical rDNA regions on chromosome 1 of sugar beet (left). At higher resolution, on interphase nuclei, clear co-hybridization of the rDNA and the TE probe indicate their association (middle). Benefitting from the higher resolution of meiotic pachytene chromosomes, clear interspersed and overlapping (yellow) signals support the co-localization of the 35S rDNA and the Galadriel retrotransposon in sugar beet (right). Reprinted from Weber et al. (2013), under CC-BY. B) To visualize the rDNA–TE association at the sequence level, error-prone genome assemblies are not suitable. Instead, long reads can be screened for co-occurrence of the rDNA and a specific TE on the same locus. Here, the association already indicated in panel (A), between the Galadriel retrotransposon and the 18S rDNA, was used. Two self-dotplots of sugar beet PacBio long reads were produced with FlexiDot (Seibt et al. 2018) and shaded to indicate the integration of the retrotransposon (pastel tones) into the rDNA (green tones). In the left instance, a canonical 18S–5.8S–26S rDNA locus is shown, in which the 18S rRNA gene is interrupted by a Galadriel retrotransposon. To the right, two rDNA repeats are arranged in an inverted orientation. Both are interrupted by Galadriel in the 18S rRNA gene. C) The 35S rDNA cluster graphs contain information about the locus: here, three RepeatExplorer-derived graphs from sugar beet are shown. On the right, a smooth, uninterrupted graph indicates that many uninterrupted, homogenized 18S–5.8S–26S rDNA monomers exist. In the middle, a disorganized, fuzzy graph with some similarities to TEs indicates TE disruption and rearrangement. To the right, the 18S–5.8S–26S rDNA locus produced a single, circular cluster. The association with TEs (in this case with the Galadriel retrotransposon also indicated in panels A and B) becomes visible as a branch emerging from the 18S rDNA region. D) An association of the rDNA and TEs often becomes visible after graphical read clustering. A shared RepeatExplorer graph indicates the sequence similarity between the 5S rDNA and retrotransposons of the Cassandra type in two species (left: *Tragopogon porrifolius*; middle: *Senecio vulgaris*). A more complex graph (right: *Musa acuminata*) indicates multiple 5S rDNA variants and sequence similarities with a Ty1/*copia* retrotransposon. Reprinted from Garcia et al. (2020), under CC-BY.

Table 1 Evidence of TE found in rDNA sequences of animals, plants, fungi, protozoans, and bacteria

Organismal group	Organismal subgroup	Organism	rDNA integration	TE type	TE superfamily	TE order/lineage	TE name	Type of evidence	Reference
Animals	Arachnids	*Hosarius adansoni*	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Degenerate PCR, cloning and sequencing	Kojima and Fujiwara (2005)
	Ascidians	*Ciona intestinalis, C. savignyi*	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2, R4	Cross genome screening, blast searches in genomic databases	Kojima and Fujiwara (2004)
	Birds	*Coturnix japonica*	Not defined	Not defined	Not defined	Not defined	Not defined	Chimeric rDNA–TE amplicons after PCR	Saifitdinova et al. (2019)
	Collembola	*Anurida maritima*	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	PCR, cloning and sequencing	Burke et al. (1998)
	Chelicerata	*Limulus polyphemus*	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	PCR, cloning and sequencing	Burke et al. (1998)
	Crustaceans	*Daphnia obtusa*	Into 28S rRNA gene	DNA transposon	piggyBac	Full DNA transposons and MITEs	PokeyA and PokeyB	Quantitative PCR (qPCR) to estimate rRNA gene and Pokey number in isolates from natural populations of *D. obtusa*, and in clonally propagated mutation accumulation lines	LeRiche et al. (2014)
		Daphnia pulex	Into 28S rRNA gene	DNA transposon	piggyBac	Full DNA transposons and MITEs	Pokey	Subcloning and sequencing	Penton et al. (2002)
		D. pulex	Into 28S rRNA gene	DNA transposon	piggyBac	Full DNA transposons and MITEs	Pokey	PCR, cloning, and sequencing upstream of Pokey insertions	Glass et al. (2008)
		D. pulex	Into 28S rRNA gene	DNA transposon	piggyBac	Full DNA transposons and MITEs	Pokey and mPok	Computational analysis of the genome assembly	Elliott et al. (2013)
		D. pulex, D. pulicaria	Into 28S rRNA gene	DNA transposon	piggyBac	Full DNA transposons and MITEs	Pokey	qPCR to estimate the number of 18S and 28S ribosomal RNA genes and Pokey elements in rDNA (rPokey), as well as other genomic locations (gPokey)	Eagle and Crease (2012)
		Daphnia species	Into 28S rRNA gene	DNA transposon	piggyBac	Full DNA transposons and MITEs	Pokey	PCR and sequencing of the Pokey integration site using a Poley and a 28S rDNA primer	Penton and Crease (2004)
		Procambarus clarkii	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Degenerate PCR, cloning and sequencing	Kojima and Fujiwara (2005)
		Triops longicaudatus	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Degenerate PCR, cloning and sequencing	Kojima and Fujiwara (2005)
	Echinoderms	*Metacrinus rotundus*	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Degenerate PCR, cloning and sequencing	Kojima and Fujiwara (2005)
	Fish	*Coregonus albula*	Into 45S	Retrotransposon	Non-LTR	LINE	Rex1	Co-localization observed after FISH	Symonová et al. (2013)
		Danio rerio	Into 5S	Retrotransposon	Non-LTR	LINE	Mutsu	RNAseq, Northern blotting, qPCR	Locati et al. (2017)
		D. rerio	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Cross genome screening, blast searches in genomic databases	Kojima and Fujiwara (2004)
		Diplodus sargus	Into the spacer of the 5S rDNA	Several retrotransposons	LTR and non-LTR	Ty3-gypsy and LINE	Not defined	Cloning, sequencing, co-localization observed after FISH	Merlo et al. (2013)
		Eptatretus burgeri	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Degenerate PCR, cloning and sequencing	Kojima and Fujiwara (2005)
		Erythrinus erythrinus	into 5S	Retrotransposon	Non-LTR	LINE	Rex3	Co-localization observed after FISH	Cioffi et al. (2010)

(continued)

Table 1 (continued)

Organismal group	Organismal subgroup	Organism	rDNA integration	TE type	TE superfamily	TE order/lineage	TE name	Type of evidence	Reference
		Gymnotus mamiraua	Into the spacer of the 5S rDNA	DNA transposon	Tc1/mariner	Not defined	Not defined	Comparative cytogenetics	da Silva et al. (2016)
		Oreochromis niloticus	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R4	Cross genome screening, blast searches in genomic databases	Kojima and Fujiwara (2004)
		O. niloticus and others related	Not defined with precision	Retrotransposon	LTR and non-LTR	SINE, Copia	SINE2-1AFC, SINE_FR2, Copia-53_MLp-1	Sequencing data	Nakajima et al. (2012)
		Oryzias lotipes	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Degenerate PCR, cloning and sequencing	Kojima and Fujiwara (2005), Kuroki-Kami et al. (2019)
		Rineloricaria latirostris	Into the spacer of the 5S rDNA	DNA transposon	hAT	Not defined	Not defined	PCR, cloning, sequencing; co-localization in FISH	Glukosky et al. (2018)
		Tanichthys albonubes	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Degenerate PCR, cloning and sequencing	Kojima and Fujiwara (2005)
		Triportheus species	Into the spacer of the 5S rDNA	Different TEs, linkage with U1 snRNA multigene family	Not defined	Not defined	Not defined	PCR, cloning, sequencing; co-localization in FISH	Yano et al. (2020)
	Insects	*Anopheles gambiae*	Not defined	Retrotransposon	Non-LTR	Not defined	Not defined	Cross genome screening, blast searches in genomic databases	Kojima and Fujiwara (2004)
		Bombyx mori	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R1, R2	Genomic screening, DNA hybridization, subcloning and sequencing	Fujiwara et al. (1984), Burke et al. (1987, 1993), Xiong and Eickbush (1988)
		Drosophila melanogaster	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R1, R2	Cloning, sequencing, genomic DNA blot analysis	Jakubczak et al. (1990, 1992)
		D. melanogaster	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R1, R2	rDNA transgenics, RNA-FISH, ChIP, RNA-seq	Luo et al. (2020)
		D. simulans	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	RNA analysis by RT-PCR (Reverse Transcription PCR), Northern blot of different crosses	Eickbush et al. (2008)
		Diadromus pulchellus, *Eupelmus vuilleti*, *Apis mellifera*	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R1, R2	Cloning, sequencing, Southern blot hybridization	Bigot et al. (1992)
		Forficula auricularia	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	PCR, cloning and sequencing	Burke et al. (1998)
		Hepialus humuli	Into the 28S–18S spacer	Retrotransposon	LTR	Gypsy	Hh Ty3/gypsyA	Sequencing, RepeatExplorer analysis, FISH	Daliková et al. (2023)
		Inachis io	Into the 28S–18S spacer	Retrotransposon	Non-LTR	LINE	IiR2	Sequencing, RepeatExplorer analysis, FISH	Daliková et al. (2023)
		Nasonia vitripennis	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R1, R2	Genomic screening, degenerate PCR, cloning, sequencing	Burke et al. (1993)
		Popillia japonica	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R1, R2	Genomic screening, degenerate PCR, cloning, sequencing	Burke et al. (1993)
		Sciara coprophila	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R1, R2	Genomic screening, degenerate PCR, cloning, sequencing	Renkwatz-Pohl et al. (1981), Kerrebrock et al. (1989)
		Tribolium castaneum	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	PCR of 5′ junctions	Eickbush et al. (2013)
	Nematodes	*Ascaris lumbricoides*	Into the 28S rRNA gene	Retrotransposon	LTR	Ty1-copia	Ty1	Sequencing of rDNA region, Southern and northern blot hybridization	Neuhaus et al. (1987)

(continued)

Table 1 (continued)

Organismal group	Organismal subgroup	Organism	rDNA integration	TE type	TE superfamily	TE order/lineage	TE name	Type of evidence	Reference
		Strongyloides rattii	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R4	Cross genome screening, blast searches in genomic databases	Kojima and Fujiwara (2004)
	Mammals	Primates (human, chimpanzee, gorilla, orangutan, gibbon, rhesus monkey)	Into IGS: fragment C (upstream rDNA promoter)	Retrotransposon	Non-LTR	SINE	Alu	Sequencing of rDNA region	Gonzalez et al. (1993)
	Mollusc	*Biomphalaria glabrata*	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R4	Cross genome screening, blast searches in genomic databases	Kojima and Fujiwara (2004)
	Reptiles	*Chinemys reevesii*	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Degenerate PCR, cloning and sequencing	Kojima and Fujiwara (2005)
	Trematodes	*Schistosoma mansoni*	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Cross genome screening, blast searches in genomic databases	Kojima and Fujiwara (2004)
Plants	Eudicots	*Beta vulgaris*	Into 18S rRNA gene	Retrotransposon	LTR	Ty3-gypsy, chromovirus, Galadriel-type	Beon	Detected in genome assembly, co-localization of 35S rDNA and TE by FISH on mitotic and meiotic chromosomes and fibers	Weber et al. (2013)
		Armeria macrophylla, A. pungens	Into 26S–18S rRNA spacer (IGS)	Transposon and retrotransposon fragments	LTR and DNA transposons	–	Sabrina and EnSpm (CACTA)	PCR, cloning and sequencing	Nieto-Feliner et al. (2019)
		Cucumis melo, C. sativus	Into ITS and ETS rDNA regions	Retrotransposon	Non-LTR	LINE	Menolird18	Co-localization of 35S rDNA and TE by FISH	Setiawan et al. (2020)
		Solanum lycopersicum	Into 18S gene	Retrotransposon	LTR	Ty3-gypsy, chromovirus, Galadriel-type	TRRTs	Co-localization of 35S rDNA and TE by fiber FISH, BAC sequencing and sequencing assembly of the rDNA units	Jo et al. (2009)
	Monocots	*Allium cernuum*	Between 26S and 18S rRNA genes	Retrotransposon	LTR	Ty1-copia	Not defined	Detected during IGS sequencing, confirmed by comparative Southern hybridization and co-localization of 35S rDNA and TE by FISH	Chester et al. (2010)
		Musa acuminata	Not defined	Retrotransposon	LTR	Ty3-gypsy, chromovirus, Galadriel-type	Monkey	Subcloning and sequencing, co-localization of 35S rDNA and TE by FISH on mitotic chromosomes	Balint-Kurti et al. (2000)
		Oryza sativa	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Cross genome screening, blast searches in genomic databases	Kojima and Fujiwara (2004)
		Zea mays	Into 28S rRNA gene	Retrotransposon	Non-LTR	LINE	R2	Cross genome screening, blast searches in genomic databases	Kojima and Fujiwara (2004)
Fungi	Ascomycota	*Ascobolus immersus*	In the ETS, separating the 26S and the 18S rRNA genes	Retrotransposon	LTR	Not defined	Hideaway	Subcloning and sequencing, comparative Sothern hybridization	Kempken (2001)
		Saccharomyces cerevisiae	Between the 3′ ends of the 37S and 5S rRNAs	Retrotransposon	Non-LTR	Ty1-copia	Ty1	Subcloning and sequencing, comparative Sothern hybridization	Vincent and Petes (1986)
	Microsporidia	*Nosema bombycis*	Particular rDNA unit: LSU-ITS-SSU-5S; integration in LSU (large subunit), ITS and SSU (small subunit)	DNA transposon	Not defined further	MITE	Four families: LSUME1, ITSME1, SSUME1, SSUME2	Whole genome sequencing (WGS) and genome-wide survey using LSU rRNA, SSU rRNA and 5S rRNA as queries; Northern blotting	Liu et al. (2013)

(continued)

Table 1 (continued)

Organismal group	Organismal subgroup	Organism	rDNA integration	TE type	TE superfamily	TE order/lineage	TE name	Type of evidence	Reference
Protozoans	Euglenozoa	*Trypanosoma brucei*	Not defined	Not defined	Not defined	Not defined	Not defined	Ordered restriction map (Bgl II fragments)	Hassan et al. (1992)
Protists	Amoebozoa	*Physarium polycephalum*	Within the coding region of the 26S rRNA gene	Not defined	Not defined	Not defined	Strain-specific group I intron	Southern blot hybridization, restriction analysis	Muscarella and Vogt (1989)
Bacteria		*Corynebacterium aurimucosum*, *Thermus scotoductius*	Into 16S rRNA gene	Not defined	Not defined	Not defined	Not defined	Analysis of genomic sequences searching for imperfect rRNA genes	Lim et al. (2012)
		Escherichia coli	Between the 16S and 23S rRNA genes	DNA transposon	Not defined	Not defined	Tn10	Lambda-specialized transducing phage, analysis of expression of tRNA and rRNA coded from genes on the phages	Morgan (1980)
		E. coli	16S rRNA and 23S rRNA	Simple TEs	Not defined	Not defined	Insertion sequences IS1 and IS2	Northern blot hybridization of probes of IS1 and IS2 to *E. coli* RNA	Nisen and Shapiro (1979)
		Mycoplasma imitans	In 16S–23S rRNA IGS	DNA transposon?	Not defined	Not defined	A transposase gene from an undetermined element	Size comparison of PCR products of the ITS region between *M. imitans* and *M. gallisepticum*	Harasawa et al. (2004)

extrachromosomal circular rDNA. As for plants, integration of TEs in the IGS has been described for *Allium cernuum*, where a Ty1/copia retrotransposon, which occurs in and outside of the rDNA arrays (Chester et al. 2010). Also, in species from the genus *Cucumis*, LINEs were detected in the internal transcribed spacers (ITS) and ETS rDNA regions (Setiawan et al. 2020). As the mentioned examples encompass animals, fungi, and plants, we conclude that TE integration in the IGS is a widespread phenomenon.

While, to our knowledge, no TE insertion has been reported within the 5S gene, TE insertions in the adjacent NTS are relatively frequent. In *Allium schoenoprasum*, for example, the insertion of a TE into the 5S rDNA spacer has led to the emergence of a second 5S rDNA family. Both 5S rDNA variants now co-exist and differ in length of the spacer (Shibata and Hizume 2002). In other plants, e.g. for the grains *Aegilops speltoides* and *Hordeum spontaneum*, En/Spm-like transposons also reside in the 5S rDNA NTS (Altinkut et al. 2006); in several banana species, Ty1/*copia*-like TE fragments also constitute a part of the 5S rDNA NTS (Hribova et al. 2010 and Fig. 3D). As for animals, we can only report examples for fish: among the TEs in the 5S spacer, DNA transposons, LINEs, SINEs, and Ty3/*gypsy* elements are the most commonly found. Remarkably, TE-flanking rRNA genes in cichlid fish have been regarded as a source of rRNA gene movement, not only for the 5S rRNA gene but also for 18S rRNA genes—generally, TE movements seem to play a large role in the generation of cichlid fish diversity (Carleton et al. 2020).

Finally, several early studies describe close relationships between a TEs and rDNAs, but without defining specifically the insertion sites or the kind of element. Examples are an unspecified mobile element in the rRNA genes of *Trypanosoma brucei* (Hassan et al. 1992), a Ty1/*copia* element in the rDNA of yeast (Vincent and Petes 1986), Ty1/*copia* intervening sequences in the rDNA of the nematode *Ascaris lumbricoides* (Neuhaus et al. 1987), or even large variations in bacterial rDNAs attributed to recent TE insertions into the 16S rRNA genes (Lim et al. 2012). Summarizing all incidents (Table 1), we conclude that TEs in rDNA occur in all major species groups—animals, fungi, plants, and even bacteria. But how do rDNAs retain the integrated TEs, are rDNAs preferred by TEs, and is an rDNA–TE association solely deleterious or can there sometimes be benefits?

Are rDNAs TE Insertion Hotspots?

Based on the observations of plant genomes, some researchers assert that the infrequent occurrences of mobile elements in rDNA point toward a rare targeting of these genes by TEs (Chester et al. 2010). Others claim that rDNA is indeed a TE insertion hotspot; in other words, TEs insert with a higher frequency in rDNA than in other genomic regions (Nieto-Feliner et al. 2019; Bendich and Rogers 2023). But which is more likely the case? First, there may be a study intensity bias, as rDNA is one of the most studied genomic loci in molecular biology. Hence, the many reported cases of TEs in rDNA may be a result of

the many research efforts spent on the rDNA. Second, as most genome assemblies are far from being complete and as the rDNA regions are difficult to assemble, we cannot yet measure universal TE integration rates in the rDNA. Nevertheless, some TE-specific rates are already available: Perez-Gonzalez and Eickbush (2001) provided an estimate of R1/R2 retrotransposition into rDNA and found it to be similar to other TEs. Hence, the rate of R1/R2 transposition into rDNA could be as similar as the rate in other genomic locations. In contrast, Redd et al. (2023) introduced the rice-derived TE mPING into yeast and found preferable mPING insertion into yeast rDNA.

Going back to the examples of R1/R2 LINEs, we discuss the impact of TEs in the rDNA on rRNA functionality. In arthropod genomes, the rRNA genes lose the capability to synthesize functional 28S rRNA genes after the invasion of rDNA by these TEs (Long and Dawid 1979; Jamrich and Miller 1984; Eickbush and Eickbush 2003). However, despite their deleterious effect, R1/R2 insertions have been maintained in arthropods by vertical transmission since the origin of this lineage (Lathe et al. 1995; Burke et al. 1998; Malik and Eickbush 1999). This does not affect the host viability as intact rDNA copies are still present—the levels of R1 or R2 insertion can vary from a small percentage to over 70% in *Drosophila* (Malik and Eickbush 1999). Interestingly, in arthropods these elements exhibit conserved insertion sites (Bigot et al. 1992; Zhang and Eickbush 2005; Eickbush and Eickbush 2012; Eickbush et al. 2013). Their precise location in the rRNA genes becomes relevant for the TE after transcription: it allows folding of the RNA in such a way that the TE-derived part is autocatalytically cut, retained, and then can enter the retrotransposition process (Oyun et al. 2018). Precise integration sites are also documented for other TEs, including LTR retrotransposons and DNA transposons (Penton et al. 2002; Jo et al. 2009). As with R1/R2 insertions, the viability of the host genome is not compromised in these cases because of the high number of (still functional) rDNA copies.

Two scenarios that are not mutually exclusive may explain these multiple precise locations: (1) the rDNA–TE associations may arise from the homogenization of a single TE insertion across the whole rDNA array, due to unequal and illegitimate recombination. As a result, many rDNA monomers with identical TE insertions would arise from a single TE integration event. (2) The rDNA–TE associations may also arise from a targeting mechanism of the TE, e.g. facilitated by a chromodomain (Gao et al. 2008; Abascal-Palacios et al. 2021). If a certain rDNA locus is targeted by a TE family with an insertion preference, multiple times, we would also observe identical TE insertions across the rDNA monomers (Jo et al. 2009; Weber et al. 2013).

Do TE Insertions in rDNA Simply Occupy a Niche for Their Own Profit or May They Even Be Beneficial to the Host?

Before discussing potential benefits of TEs being integrated into rDNA, it should be noted that there is still too little information to completely ascertain whether rDNA–TE associations are coincidental or may indeed provide a benefit onto which selection can act upon. Most TEs can also integrate into other locations (not just into the rDNA), hence the impact on the host fitness may be an important aspect to evaluate if an rDNA–TE association will be sustained across generations. That said, as rRNA genes are multicopy, actively transcribed and highly conserved, it is clear that a TE insertion in rDNA ensures its transcription and propagation. Hence, the rDNA can be considered a "ideal niche" for TE insertion. This niche would provide a safe haven for TEs, from which they propagate (Penton et al. 2002). In turn, as a repetitive multigene family, there are many more copies of rDNA than those that are essential. Thus, rDNA-integrated TEs can exist up to a certain threshold without important phenotypic effects which may hinder the host fitness (Eickbush and Eickbush 1995; Malik and Eickbush 1999), as intact rDNA copies would still be available. Besides, TE insertions into conserved, but non-essential regions, ensure the integrity and functionality of rDNA genes of the respective monomer. This preference likely allows the TE to "survive" (and also thrive) in rDNA loci, as strong selection against disrupted and inactive rDNA units would eliminate them from the genome. However, there is also a danger for TEs in integrating into the rDNA. Due to rDNA's homogenization processes (concerted evolution), TE insertions in rDNA may also be lost more quickly than in other genomic regions. Hence, the rDNAs capacity for quick homogenization is a double-edged sword for TEs. It allows quick spread and also quick removal, as proposed earlier by Perez-González et al. (2003).

Are there also benefits for rDNA regulation of the host brought by TEs? First, TEs may serve as a vehicle to transpose rDNA from one genomic location to the other. This may be advantageous in some karyotypes, which suffer from frequent chromosome rearrangements. Second, transposition can inactivate supernumerary rDNA copies, which may be helpful to better regulate a gene dosage, e.g. after polyploidization or horizontal transfer. A close association of inactive heavily mutated rDNA units with TEs has been reported in plant allopolyploids (Handa et al. 2018; Tulpová et al. 2022) and in alien rDNA following horizontal transfer (Mahelka et al. 2017). In these instances, TEs may accumulate in those rDNA loci (units) which are already inactive and have lost homogenization capacity. Beneficial roles of TEs may also be indirect. For example, in *Drosophila*, the rDNA-specific R2 endonuclease introduces double-strand breaks within the rDNA, which immediately serve as a starting point for rDNA homogenization, maintenance, and copy number upholding (see above). Similarly, a regulatory function of TEs (McClintock 1951) that allows the neighboring rDNA chromatin to benefit from the epigenetic machinery of TEs cannot be excluded.

Considering all the points above, it becomes clear that only TEs in conserved but non-essential rDNA sites stand a chance of long-term survival, proliferation, and spread in the rDNA. This leads to few rDNA landing sites that may have a chance of becoming preferred TE hotspots. All these aspects point to

Table 2 Evidence of rDNA-derived TE sequences

Organismal group	Organismal subgroup	Organism	Similarity to which rDNA	TE type	TE superfamily	TE name	Reference
Animals	Crustaceans	*Daphnia pulex*	Region of the IGS in internal region	DNA transposon/ MITE	piggyBac	Pokey and mPok	Elliot et al. (2013)
	Fish	Salmonoidei	5S rDNA promoter	Retrotransposon	SINE	OS	Matveev and Okada (2009)
		Danio rerio	5S rDNA promoter	Retrotransposon	SINE	SINE3/AmnSINE1	Kapitonov and Jurka (2003)
	Insects	Several species	5S rDNA promoter	Retrotransposon	SINE	HaSE3	Wang et al. (2012)
	Mammals	Several species	5S rDNA promoter	Retrotransposon	SINE	OS	Nishihara et al. (2006)
		Megachiroptera	5S rDNA promoter	Retrotransposon	SINE	MEG-RL, MEG-RS, MEG-TR	Gogolevsky et al. (2009)
		Pedetes capensis	5S rDNA promoter	Retrotransposon	SINE	Ped-1	Gogolevsky et al. (2009)
		Homo sapiens	28S rDNA	Retrotransposon	SINE	SINE28	Longo et al. (2015)
	Nemerteans (ribbon worms)		rDNA: 5S rDNA promoter	Retrotransposon	LTR/TRIM	Ajax	Kojima (2024)
	Reptiles	*Anolis carolinensis*	5S rDNA promoter	Retrotransposon	SINE	5S-Sauria	Piskurek et al. (2009)
Plants	Angiosperms-eudicots	Amaranthaceae	5S rDNA promoter	Retrotransposon	LTR/TRIM	Ama_Cassandra	Maiwald et al. (2021)
		Asteraceae	5S rDNA promoter	Retrotransposon	LTR/TRIM	Cassandra	Maiwald et al. (2024)
		Several species	5S rDNA promoter	Retrotransposon	LTR/TRIM	Cassandra	Gao et al. (2016)
		Several species	5S rDNA promoter	Retrotransposon	LTR/TRIM	Cassandra	Kalendar et al. (2008)
		Rosaceae	5S rDNA promoter	Retrotransposon	LTR/TRIM	Cassandra	Yin et al. (2014)
		Several species	5S rDNA promoter	Retrotransposon	LTR/TRIM	Cassandra	Kalendar et al. (2020)
		Brassicaceae	5S rDNA promoter	Retrotransposon	LTR/TRIM	Cassandra	Sampath and Yang (2014)
	Angiosperms-monocots	Agavaceae	5S rDNA promoter	Retrotransposon	LTR/TRIM	Cassandra	Tamayo-Ordóñez et al. (2018)

tightly linked co-evolution between TEs and rDNA, in which the TEs *evolve to select* the most appropriate regions to insert into, whereas the rDNA's homogenization capacity *removes* the potentially harmful insertions from the genome. Hence, we speculate that more complete sequencing and assembly of rDNA loci may bring to light more TE integration hotspots at distinct sites within the rDNA monomers. Whether the TE ratio in rDNA outshines other iconic chromosomal regions, such as the telomeres and centromeres, remains to be seen (and is likely organism-specific).

Ribosomal DNA in TEs

Several studies have detected ribosomal DNA fragments in TEs (Table 2). In general, TEs have a tendency to acquire sequence modules and protein domains by reshuffling (e.g. Jiang et al. 2004; Seibt et al. 2020). In some of these cases, TEs have likely co-opted and domesticated certain domains (reviewed by Cosby et al. 2019; Wang and Han 2021). The most common rDNA genes or fragments found associated with TEs are 5S ribosomal DNA sequences. TEs containing 5S sequences usually keep, more or less intact, the internal 5S RNA promoter for Pol III for the TE's proliferation benefits. Escaping from the boundaries of Pol II transcription (typical for TEs and genes) and instead opting for the Pol III promoter enables the TE to unlock a completely different proliferation strategy, at different time points and likely in different tissues as opposed to the typical Pol II-transcribed TEs. In the first release of SINEBase, a database of short interspersed elements (SINEs) (Vassetzky and Kramerov 2013), 5S-derived SINEs accounted for 2.3% of its content and to date, they are known in reptiles, insects, fish, and mammals.

To our knowledge, there are no 5S-derived SINEs in plants. Instead, plants harbor non-autonomous LTR retrotransposons with 5S rDNA promoter sequences in their LTRs, named Cassandra (Kalendar et al. 2008, 2020; Maiwald et al. 2021, 2024; a recent study also found analogous retrotranspons in ribbon worms, named Ajax (Kojima 2024)). Cassandras were first described in 50 plant species including ferns, monocots, and eudicots and later (re)confirmed in several angiosperm lineages (Yin et al 2014; Gao et al. 2016; Kalendar et al. 2020), including *Arabidopsis* (Sampath and Yang 2014), *Agave* (Tamayo-Ordóñez et al. 2018), and beets (Maiwald et al. 2021). At present, there are no reports of Cassandras in gymnosperms. Looking closely at the Asteraceae, the plant family with most variability in the 5S rDNA, including rDNA arrangements (Garcia et al. 2010) and promoter shifts (Garcia et al. 2012), Maiwald et al. (2024) found that Cassandra

retrotransposons closely mimic the promoter motif changes, thus providing a recent example of rDNA–TE co-evolution.

In some cases, Cassandra TEs show a tandem-array pattern, reminiscent of cellular 5S (Kalendar et al. 2008; Maiwald et al. 2021). This arrangement has been used to explain the very variable distribution of 5S rDNA loci along plant chromosomes, in which Cassandra signals would have been confused with authentic 5S rDNA loci in FISH experiments. Indeed, cases with extraordinarily high numbers of 5S loci have been detected (for example, up to 71 loci in tulip genomes; Mizouchi et al. 2007) that could likely be Cassandra elements accounting for these possibly "fake" rDNA loci numbers. A similar situation might apply for the 22–38 5S rDNA loci for *Alstroemeria* (Kamstra et al. 1997; Baeza et al. 2007) or 10–38 for *Paphiopedilum* (Lan and Albert 2011), considering that the median for angiosperms is two 5S sites (one locus; Garcia et al. 2017). For the latter genus, the authors already proposed that TE activity may underlie the surprisingly high 5S loci number, i.e. some of the 5S signals may result from pseudogenes that were mobilized by TEs (Lan and Albert 2011). TEs also harbor other rRNA genes or fragments such as the mammalian SINE28 that contains 28S rDNA fragments (Longo et al. 2015). Similarly, Pokey TEs possess a series of 200 bp repeats upstream of the transposase domain, derived from the rDNA IGS (Elliott et al. 2013).

The many cases of rDNA-related acquisitions inside TEs are likely the result of modular reshuffling as has been often observed in TE evolution (e.g. Wollrab et al. 2012; Seibt et al. 2020), especially for non-autonomous elements. While we speculate that most rDNA-related sequence modules do not benefit the TE, some may make a difference toward the TE's evolutionary success—such as the 5S rDNA promoter. These successful acquisitions are seen several times across the tree of life, for instance in animals and plants, benefitting different TE families, including the iconic Cassandra retrotransposons.

Future Perspectives

We have shown that rDNAs and TEs are two important actors in genomes and have both similarities and differences in terms of their organization, function, evolution, and mobility. Interactions between both have been described and these can contribute to their mutual evolution and genomic distribution. This landscape of rDNAs and TEs in the genome is a mixed one, with the interplay between their organization, evolution, and function leading to a diverse range of outcomes.

What to Expect From Current and Next Technical Advancements

The advancements of the long-read technology have the potential to provide even more insights into the complex interplay between rDNA, TEs, and the genome as a whole. Long reads capture longer stretches of repetitive DNAs in a single read, hence reducing the need for assembly and improving the accuracy of analysis (Marx 2023). This approach has meant a huge step forward since the repetitiveness and complexity characterizing both rDNA and TE-rich regions were a big handicap for previous sequencing technologies based on much shorter reads. Long reads can reveal the precise and (if present) the higher-order organization of rRNA genes, as done by Havlová et al. (2016), Symonová et al. (2017) and Heitkam et al. (2020), and the respective positions of rDNA and TE (Fig. 3B). Recently, McKinlay et al. (2021) went one step further using a target enrichment method to enrich for rDNA loci in ultra-long Oxford Nanopore Technology sequencing reads, given that these loci usually represent a small proportion of the genome; a similar approach, but for TEs, was followed by Merkulov et al. (2023). Research in TEs may be perhaps the most affected field by the availability of long reads (Shahid and Slotkin 2020), given their intrinsic and enormous diversity, although advances in long-read sequencing may also be the key to finally and precisely assessing sequence, structure, and copy number variation of rDNA (Hall et al. 2022). Overall, the dropping cost of even the most sophisticated omics approaches and the new analytical tools that are continuously arising will surely also allow a more detailed examination of the relationships between rDNAs and TEs.

Apart from resolving repetitive loci by long-read sequencing, optical mapping technologies have the capability to provide high-resolution images of entire chromosomes including the highly repetitive ribosomal loci. Thus, optical mapping can inform about the structure and organization of ribosomal DNA and TEs, by allowing the visualization of their distribution and orientation (Tulpová et al. 2022). Genome editing based on CRISPR/Cas9 may also be used in the study of repeats such as rDNA and TEs, by enabling their targeted modification and maybe even deletion from distinct sites (Smith et al. 2020; Lopez et al. 2021). Changing the overall location of rDNA and TEs may be also possible in the near future using chromosome modification techniques (Schmidt et al. 2020). Summarizing, we predict that in the near future, genome sequencing and mapping, as well as editing technologies, will likely produce the largest gain of knowledge in unraveling the rDNA–TE associations.

Biological Roles and Consequences of the rDNA–TE Interplay

Beyond genome structure and evolution, research on ribosomal DNA and TEs also contributes to the understanding of many biological processes, such as rDNA maintenance, control of copy numbers, and even more complex processes such as aging and senescence. Regarding rDNA maintenance, a retrotransposon-induced mechanism was recently reported in *Drosophila* (Nelson et al. 2023) and perhaps other insects. It remains to be determined whether similar mechanisms operate in other groups, such as plants, whose genomes are inherently known to be thronged with TEs. If so, this would pave a way to studies of potential of beneficial effects of TEs on host fitness as a driving force behind their success across different organisms.

Similarly, new structural links between rDNAs and TEs are arising. Both components also can exist beyond the chromosomes, for example as extrachromosomal circular DNAs (eccDNAs; Flavell and Ish-Horowicz 1981; Pont et al. 1987; Cohen et al. 2003, 2008). These DNA rings mostly originate from recombinational processes and play roles in upholding rDNA copy number (Mansisidor et al. 2018). Regarding TEs, eccDNAs can be side-products (Lanciano et al. 2017; Mann et al. 2022; Peng et al. 2022) or even necessary intermediates for the mobilization of TEs (Yang et al. 2023). In the framework of this review, eccDNAs are interesting to explore, as both—some rDNAs and some TEs—may acquire mobility, if present in circular form. Further eccDNA study may likely bring to light more insight into rDNA–TE associations.

On a physiological level, rDNAs are associated with cellular aging, as the accumulation of rDNA mutations over time can affect cellular function and contribute to age-related decline (Sinclair and Guarente 1997; Kasselimi et al. 2022). Loss of rDNA repeats, possibly through rDNA circle formation and accumulation, is associated with lifespan in both yeast and humans (Goffová and Fajkus 2021). Despite its importance for maintaining all cellular functions, rDNAs become increasingly fragile with age, and are prone to copy number and DNA methylation changes (Watada et al. 2020). TEs also influence aging processes, as their epigenetic control becomes more unstable with increasing age, resulting in increasing TE transcript levels, gene regulatory change, and more transposition (Gorbunova et al. 2021; Yang et al. 2022; Yushkova and Moskalev 2023). Concluding, aging profoundly affects both rDNA and TEs. Meanwhile, also rDNA and TEs affect aging, on at least two levels: DNA methylation and regulatory control as well as mobility and copy number variation. Hence, with aging, these seemingly opposite genomic components can both serve as starting points of chromosomal instability, thus speeding up the cellular trajectory toward mortality. We expect that the next decade will provide molecular insights into the role of TEs and rDNAs in aging, and that regulatory control of both repetitive genome components likely plays a role in identifying targets for intervention and treatment of age-related diseases.

Conclusion

Despite the perceived disparity between rDNAs and TEs, both genome components share more than both being discovered in maize by Barbara McClintock. We outline the many examples, where TEs and rDNAs co-occur, interact, benefit, and even evolve together. We outline what to expect from the latest technical advances and tap into the shared biological roles of rDNAs and TEs. Starting out as seemingly antagonistic forces—with rDNAs as housekeepers upholding cell maintenance and TEs as silenced disruptive agents—rDNAs and TEs often cross paths. However, with passage through the cell's lifespan, their genomic effects converge, both leading toward genomic fragility. We conclude that the often-overlooked interplay of rDNAs and TEs is a major force not only in genome evolution but also in cellular maintenance, gene regulation, and chromosomal stability.

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Data Availability

Not applicable.

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