RESEARCH ARTICLE

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PIWI protein-interacting RNA pathway – an adaptor for the exaptation of transposable elements

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ABSTRACT

Transposable elements or transposons (TEs) are abundant genome components in almost all multicellular organisms. Their activity is double-sided: they could be harmful and destructive for the genes and genomes, and yet could carry beneficial information (new regulatory motifs, new lncRNA and protein-coding genes, etc.) The host response to this double-sided nature of TEs is the evolution of various systems for TE silencing and control at DNA, transcriptional and post-transcriptional level. TE control systems neutralize the harmful effects of TEs and help the beneficial traits of TE sequences to be integrated into the host genome and become part of cellular signaling or regulatory systems. So the co-evolution between TEs and TE control systems could be considered the main road to TE exaptation and functionalization. The main focus of this review is the complex interplay between TEs and PIWI/piRNA system, an ancient regulatory system in animals, active mostly in the germline and early embryo. The roles of TEs, PIWI/piRNAs, and their interactions are discussed in more detail in two fields that together are crucial for evolution itself: animal reproduction and stress response.

Key words: transposons; PIWI interacting RNAs; PIWI proteins; co-evolution; germline; transposon exaptation; stress response

Introduction

The transposon dualism: good or bad are transposons?

Transposon sequences could carry information about order and function, as well as about chaos and destruction. TE sequences encode many "ready to use" motifs for gene regulation and function: promoters, TF binding sites, miRNA target sites, splicing signals, lncRNA, and protein domains. At the same time, they are powerful agents of chaos causing all sorts of mutation events at all possible scales – point mutations, deletions, insertions, recombinations, chromosome rearrangements, and massive increases in genome size... This TE dualism is broadly discussed and reviewed in the literature (prominent examples: Britten & Davidson, 1971; Kidwell & Lisch, 2001; Kazazian, 2011; Shapiro, 2011; Dubin et al., 2018).

Most TEs have virus-related origin (Koonin et al., 2011), although there is no consensus on whether transposons have originated from viruses or vice versa (Mustafin, 2018). Both entities are quasi-autonomous and share many sequence features, genes, and proteins. Transposons and viruses, however, have distinct evolutionary strategies. Although regarded as selfish DNA (Orgel & Crick, 1980), transposons are not completely selfish: they are not infectious (despite increased probability for horizontal transfer compared to regular genes (Schaack et al., 2010) and cannot leave their host, so TEs are more dependent on the host's fitness and reproduction for their survival than viruses (Cosby et al., 2019). Most TEs and TE families have adapted to pose minimal harm to genomes, and some have even become obligate mutualistic entities. Relationships between TEs and genomes extend to a continuum between parasitism and obligate mutualism (Kidwell & Lisch, 2001) And the host systems for transposon control are the main factors helping TEs to find their place in this continuum and eventually, to move towards the mutualistic side.

Systems and mechanisms for transposon control

There is a rich variety of systems for transposon control and silencing in all living organisms. Here I discuss only the defense systems in eukaryotes.

***At DNA level*:** In vertebrates, APOBEC (apolipoprotein B mRNA editing enzymes, catalytic polypeptide-like) is a protein family of DNA cytidine deaminases responsible for a specific pathway of TE repression - **DNA editing**. The concept of DNA editing challenges the central dogma of "read-only" properties of DNA information. (Knisbacher et al., 2016) APOBEC family of enzymes convert cytosines in DNA to uracils (C-to-U) and the result is hypermutation. The editing of DNA occurs mainly in immunoglobulin genes but it has been expanded on retrovirus and retrotransposon sequences as well. The many introduced mutations render TEs inactive (Chiu & Greene, 2008; Knisbacher & Levanon, 2016;

Knisbacher et al., 2016). However, there are occasions where edited TEs are preferentially retained in active genome regions and could become positively selected, useful sequences (Suh et al., 2018).

At the transcription level (transcriptional gene silencing, TGS: TEs are silenced by various **repressive epigenetic modifications** (Slotkin & Martienssen, 2007): heterochromatization and ATP-dependent nucleosome remodeling (Bartholomew, 2014), repressive histone modifications (Kondo & Issa, 2003; Martens et al., 2005), and DNA methylation. Various defense systems based on small RNAs and/or proteins attract DNA methylation and repressive histone marks to TE sequences (Law & Jacobsen, 2010). In plants, DNA methylation of TEs is achieved through the process of siRNA-directed DNA methylation, or RdRM (He et al., 2014) In animals, two main systems control TE activity: the Piwi-interacting RNA pathway (Clark & Lau, 2014; Tóth et al., 2016; Sun et al., 2022), and KRAB-ZPF transcription factor regulation (Ecco et al., 2016; Yang et al., 2017).

At the post-transcriptional level (post-transcriptional gene silencing, PTGS) ADARs (adenosine deaminases acting on RNA) are a family of enzymes that bind to double-stranded RNA (dsRNA) and catalyze the conversion of Adenosines to Inosines (**A-to-I RNA editing**) The vast majority of the A-to-I RNA editing occurs within repetitive elements, in particular in SINE (Alu in primates) inserted in various noncoding regions of mRNAs (introns and UTRs) in tandem and inverse orientation (Kim et al., 2004). The consequences can be repression and restriction of TE mobility, formation of altered protein, or change in RNA metabolism) (Athanasiadis et al., 2004; Nishikura, 2016; Orecchini et al., 2017; Frassinelli et al., 2021).

Other major players in the PTGS control over TEs are various **small RNA-based response systems**: RNA interference (RNAi) in plants and invertebrates (Obbard et al., 2009), microRNAs, and again, the Piwi-interacting RNAs and PIWI proteins which can act both at the transcriptional and post-transcriptional level (Lim & Kai, 2015). These systems resemble CRISPR-Cas mediated genome immune system in bacteria (Takahashi et al., 2021), with small RNAs recruiting effector proteins with endonuclease activity and guiding them to the complementary target RNA sequence which is then cleaved or its translation is repressed (Wheeler, 2013).

In this review, I focus on the interactions between TEs and the Piwi-interacting RNA pathway. In the following sections, I briefly discuss the basis of piRNA biogenesis and function, as well as the two most important from the evolutionary point of view fields of TE-piRNA/PIWI interaction: gametogenesis and early embryonic development, and stress response.

Piwi-interacting RNAs and PIWI proteins – a brief overview

PIWI-interacting RNAs (piRNAs), microRNAs (miRNAs), and small interfering RNAs (siRNAs) are the three main classes of small non-coding regulatory RNAs in eukaryotes. While siRNAs and miRNAs have broader phylogenetic distribution, piRNAs are found only in metazoans except in a few non-typical cases in ciliates (Lim & Kai, 2015). The Argonaute family proteins are the key effector molecules in siRNA, miRNA, and piRNA silencing pathways (Meister, 2013). The family includes two subfamilies (clades): AGO and PIWI. While siRNAs and miRNAs partner with the AGO clade proteins, piRNAs are loaded onto proteins of the PIWI clade (Aravin et al., 2006). The biogenesis and function of si-, mi- and piRNAs share many common features, but there are also important differences (Table 1) (Cerutti & Moll Casas-Mollano, 2006; Vagin et al., 2006; Wheeler, 2013; Ozata et al., 2019; Zhang, J. et al., 2022).

Table 1. *Comparison between the three main classes of small regulatory RNAs in eukaryotes*

Small RNA class	Length (nt)	Source (S), Target (T)	Pre-cursor	Sequence conservation /distribution	Maturation factor	Argonaute partner	Mode of action
siRNA	21-24	**S:** Exogenous and endogenous virus-like sequences; **T**: same as S	dsRNA	Low (higher for esiRNAs)/ plants, invertebrates	DICER	AGO clade	TGS (RDRM) and PTGS (RNAi, target cleavage)
miRNA	21-22	**S**: Endogenous miRNA genes; **T:** endogenous mRNAs, some TE-related RNAs	Stem-loop ssRNA	High/all eucaryotes	DICER	AGO clade	PTGS (translation repression)
piRNA	22-34	**S:** endogenous piRNA clusters; **T:** TEs, TE containing mRNAs, other mRNAs, pseudogenes, telomeres, etc.	Long ssRNA	Low/multicellular animals (Metazoa)	Other endo-nucleases, incl. PIWI	PIWI clade	TGS (attracting epigenetic modifications), PRGS (mRNA cleavage)

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The genomic piRNA loci (or piRNA clusters) tend to be enriched in old and fragmented TE sequences (TE graveyards (Chung et al., 2008). The piRNA maturation is Dicer-independent and may involve different endonucleases in different taxa, including PIWI proteins themselves.

piRNAs are generated by two distinct molecular mechanisms, each related to a particular mode of piRNA activity (TGS or PTGS):

- **primary pathway** in the nucleus: transcription of piRNAs from piRNA clusters, processing, loading the piRNAs onto PIWI proteins, and piRNA guided silencing via epigenetic modifications of TEs and other sequences (reviewed in Lim & Kai, 2015)
- **secondary pathway** (or "ping-pong" cycle) in the cytoplasm (more precisely, in the nuage or germplasm, a membraneless organoid surrounding the nucleus of the germ cells (Castañeda et al., 2011; Czech & Hannon, 2016; Gainetdinov et al., 2018). This pathway leads to fast amplification of piRNAs which guide PIWI subfamily proteins to their targets (TE RNAs, mRNAs with inserted TE fragments, and other mRNAs), cleavage, or repression of the target RNAs (PTGS).

The main field of piRNA activity is germ cells, early zygote, and stem cells (Sun et al., 2022), although there is a growing number of studies showing PIWI proteins and piRNAs functioning in other somatic cell types (Peng & Lin, 2013; Ross et al., 2014; Kim, 2019) and being related to cancer and other diseases (Shirzad, 2021; Zhang, T. et al., 2022).

As these and many other studies have revealed, piRNA/PIWI pathway function extends far beyond control over TEs. Yet, their main functions are based on their interplay and co-evolution with TEs. Further in this review, I focus on the fields that are most crucial to evolution: reproduction (gametogenesis and early embryonic development), and stress response.

PIWI/piRNA pathway and TEs in gametogenesis and early embryonic development

TEs strongly prefer to transpose and express in the germline. There are ideas that sexual reproduction is an instrument for spreading of (mostly deleterious) TEs (Wright & Finnegan, 2001); moreover, TEs have been linked to the origin of sexual reproduction itself (Hickey, 1993; Arkhipova, 2005). So first, TE transposition in the germline is a way to guarantee their vertical transfer between generations (Dechaud et al., 2019). Second, restricting the transposition mainly in the germline is safer for both TEs and host as far as it doesn't affect fertility (Charlesworth & Langley, 1986; Cosby et al., 2019). In turn, PIWI/piRNAs are also active mainly in germ cells. Germline piRNAs from various metazoans target TEs, but they also regulate other mRNAs not (obviously) related to TEs (Wang & Lin, 2021). The name of the PIWI subfamily of proteins itself comes from its founding member in Drosophila, the piwi gene (abbreviation of "**P**-element **i**nduced **wi**mpy testis"; P-element is an active DNA transposon in fruit fly) (Lim & Kai, 2015). Mutations in PIWI proteins have been linked to male or female sterility in many species like Drosophila, zebrafish, xenopus, mouse, rat, and human (Lau et al., 2006; Carmell et al., 2007; Houwing et al., 2008; Yuan & Zhao, 2017; Hasuwa et al., 2018).

The germline and the early embryo are the main arena of the interplay between TEs and PIWI/piRNAs. Most probably, PIWI/piRNA pathway has evolved in the gonads as an additional control mechanism against TE activity. (Brennecke et al., 2007; Armisen et al., 2009; Kawaoka et al., 2009; Mani & Juliano, 2013). On the other hand, gametogenesis and early embryonic development in animals are strongly dependent on exapted TEs for their proper function (Cosby et al., 2019; Senft & Macfarlan, 2021). So PIWI/piRNA pathway could relate TGS and PTGS mechanisms and various protein factors in a crucial junction to maintain the delicate balance between regulated TE activity and dysfunctional TE overexpression (Figure 1).

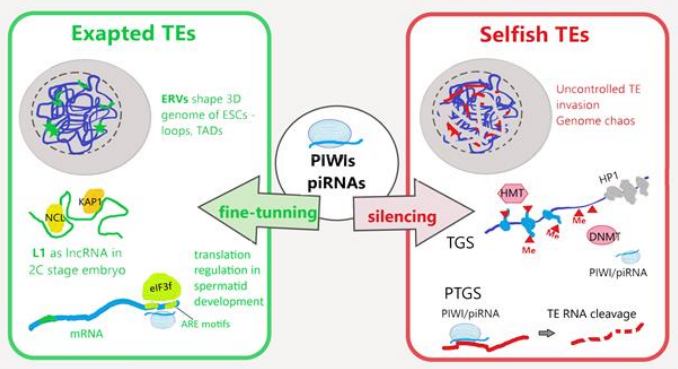

Figure 1. *PIWI/piRNAs and TEs in germline and embryo development. The figure illustrates the balancing and adaptor roles of PIWI/piRNAs, fine-tuning the activity of beneficial, exapted TEs and silencing of damaging and overexpressed TEs. The scheme illustrates some of the discussed examples of TEs exapted in germ cells and embryo development and the basic PIWI/piRNA related mechanisms for uncontrolled TE silencing. TADs - topology associated domains, NCL - nucleolin, HMT – histone methyltransferase, DNMT – DNA methyltransferase, HP1 – heterochromatin protein 1*

Important examples of piRNA/PIWI activities in animal reproduction and early embryogenesis are discussed below.

PIWI/piRNAs and TEs in gametogenesis

Epigenetic reprogramming. In early embryogenesis, before and soon after the gastrulation, the germ cell precursors (or primordial germ cells, PGCs) migrate toward the region of the future gonad (Castañeda et al., 2011). During their journey, PGCs undergo loss of repressive DNA methylation marks

(Seki et al., 2005) – "epigenetic reprogramming". During this period PGCs return to a pluripotent state, and reprogramming establishes a clear genome on which the sex-specific imprints of the embryo could be painted (Kafri et al., 1992; Extavour & Akam, 2003). The de-methylated chromatin state leads to temporary TE activation (Morgan et al., 2005; Leung & Lorincz 2012). The de-methylation window extends for a few days, and then de novo methylation is established, to restore the control over TEs and to prevent DNA damage from the transposition. DNA methylation is mediated by the DNA methyltransferases (DNMT), which cooperate with the piRNA pathway for de novo TE DNA methylation (Aravin et al., 2008; Kuramochi-Miyagawa et al., 2008) (Figure 1). TE regulation is crucial to secure a sufficient level of TE expression during the reprogramming stage of gametogenesis and to stop TEs hyper-activation. However, the specific functions of TE expression in epigenetic reprogramming, as well as the evolutionary forces for their selection are still unknown. (Russell & LaMarre, 2018).

Gamete stem cells establishment, renewal, and differentiation. PIWI/piRNAs are vital for these processes (Houwing et al., 2008; Zhao et al., 2013; Perillo et al., 2023). Inactivation of the PIWI/piRNA pathway in germline differentiation causes genomic instability and meiosis arrest in both sexes due to uncontrolled overexpression of TEs, especially L1 and ERV (Carmell et al., 2007; Kuramochi-Miyagawa et al., 2008) (Figure 1).

Independently of piRNA, MILI (one of the three PIWI homologs in mouse) is required for translational up-regulation of specific genes during the germline stem cell self-renewal in the mouse testes (Unhavaithaya et al., 2009; Rojas-Ríos et al., 2017). In mouse spermatocytes and spermatids, a fraction of piRNAs associate with MIWI (another PIWI homolog) and imperfectly target ARE motifs (ARE=AU-rich element, a motif often carried by TE sequences) in the 3′ UTRs of target mRNAs (Figure 1). The translation initiation factor eIF3f also binds to the target mRNAs and forms a complex with piRNA and MIWI to further activate the translation of mRNAs, required for acrosome formation during spermatid development (Dai et al., 2019).

In Drosophila ovarian cell cultures, TE insertions around lncRNA stimulate the expression of corresponding lncRNAs in a Piwi-dependent manner (Sytnikova et al., 2014, Dodson & Kennedy, 2019). These examples imply a possible role of piRNA in *positive* transcriptional regulation of protein and lncRNA expression, which challenges the usual idea of piRNAs as repressive regulators.

PIWI/piRNAs and TEs in early embryogenesis

Maternal-to-zygotic transition (MZT) and trans-generation epigenetic memory. After fertilization, the genome of the zygote is silent in the early embryo, so the maternal mRNAs entirely coordinate and regulate the first steps of development. Gradually, maternal mRNAs are eliminated and the zygotic genome becomes activated and expressed, and finally takes control over development - a process called maternal-to-zygotic transition (MZT) (Ramat & Simonelig, 2021).

Some TE families like LINEs and ERVs are tightly intertwined with MZT. For example, MERVL and HERVL appear to contribute to zygotic genome activation in mice and humans (Macfarlan et al., 2012; Hendrickson et al., 2017).

PIWI/piRNAs have a crucial function in maternal mRNA decay during the MZT. In Drosophila early embryos, maternally deposited piRNAs produced from two TEs, roo and 412, target the 3′ UTR in the mRNA of the nanos (nos) protein, an important morphogen. The partial and regulated nos mRNA decay is necessary for gradient formation from the posterior to the inferior part of the embryo and proper head formation in later embryonic development (Rouget et al., 2010; Trcek et al., 2015). As an efficient system to degrade mRNAs, the piRNA pathway might have been coopted to provide an additional level of mRNA decay during the MZT and increase the robustness of the process (Ramat & Simonelig, 2021).

The participation of the piRNA pathway in transgenerational epigenetic effects in Drosophila was also demonstrated in studies on hybrid dysgenesis - a phenomenon in which maternally deposited piRNAs repress P- or I-element TEs and rescue the progeny from defects caused by their transposition (Castro & Carareto, 2004). Maternally deposited piRNAs are required to establish the piRNA ping-pong cycle to generate sufficient levels of piRNAs to silence TEs in embryo with PTGS, which cannot be fully achieved with the primary pathway of piRNA production from the embryo piRNA clusters alone (Chambeyron et al., 2008)

Supporting totipotency of embryonic stem cells. Human embryos express TEs from various classes including L1, Alu, SVA, and HERV-K (Huda et al., 2010; Guo et al., 2014; Grow et al., 2015). There is growing evidence that ERVs are key factors in supporting totipotent and pluripotent cell states. For example, MERVL transcription in the mouse embryo triggers the formation of hundreds of chromatin loops that fold the genome into unique 3D architecture crucial to totipotency (Kruse et al., 2019). In human ESCs, HERVH is highly expressed in pluripotent cell populations and promotes the formation of chromatin loops and topological domains unique to ESCs (Ohnuki et al., 2014; Wang et al., 2014; Göke et al., 2015) (Figure 1). HERVS also promote the expression of chimeric long noncoding RNAs (lncRNAs) Experimental inactivation by RNAi or CRISPR of some of these HERVH-derived lncRNAs in induced PSCs (iPCSs) results in the loss of pluripotency and increases their capacity to differentiate (Kapusta et al., 2013; Wang et al., 2014, reviewed in Cosby et al., 2019).

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The transition between developmental phases. The precise transcriptional activation of L1 retrotransposon in preimplantation embryos is required for the developmental progression in mouse. Nuclear L1 RNAs behave as functional lncRNA and probably work by forming a RNP complex with at least two host proteins, Nucleolin and KAP1. This interaction initiates a regulatory cascade that stimulates the exit from the 2C developmental stage (Honson & Macfarlan, 2018; Percharde et al., 2018). Interestingly, Nucleolin was shown previously to bind human L1HS RNA, so these events could well extend beyond the mouse embryo (Peddigari et al., 2013) (Figure 1).

Overall, regulated TE expression is needed for normal embryogenesis, while dysregulated reintegration and overexpression of TEs during reprogramming poses significant risks to the genome. In this entangled network of relationships, PIWI/piRNA pathway could have expanded its repressive role to more fine-tuned regulatory activities towards exapted TEs in the germline and early embryo. PIWI/piRNA pathway could acquire an important role in the keeper of the balance between regulated beneficial TE activities and uncontrolled overexpression of TEs (Figure 1).

Convergent processes in plants – phased siRNAs

The importance of small RNA pathways similar to PIWI/piRNAs in gametogenesis and embryo development is demonstrated via an intriguing example of **convergent evolution between plants and animals – the development of plant reproductive phased siRNAs (phasiRNAs)** (Zhai et al., 2015; Komiya, 2017; Liu et al., 2020; Nie et al., 2023). Despite their unrelated origin in plants and animals, respectively, phasiRNAs and piRNAs share a striking number of similarities, including enrichment in male reproductive organs and function in male fertility, activity in both premeiotic and meiotic pathways, phasing, and roles beyond reproductive tissues (Liu et al., 2020; Ozata et al., 2019). The main difference between plant phasiRNAs and animal piRNAs is that the latter function in the suppression of TEs while plant phasiRNAs do not, probably because of the existence of an additional small RNA pathway for TE control in plants – the Pol IV siRNA pathway (Han et al., 2015; Liu et al., 2020).

Stress response, TEs and PIWI/piRNAs

One of the first ideas for the global function of TEs as genome stress sensors are proposed by their discoverer B. McClintock (McClintock, 1947; McClintock, 1984). Since then, numerous research projects had investigated in detail the relationships between transposons and stress response in plants and animals (Capy et al., 2000; Hunter et al., 2015; Miousse et al., 2015; Negi et al., 2016; Lanciano & Mirouze, 2018; Ramakrishnan et al., 2021 among many others). In recent years, it becomes clear that the relationship between stress and TEs is complex and depends on the life phase of the cell (De Cecco et al., 2013), the type of TE, and the type of stress (Horváth et al., 2017). The stress response can be accomplished at DNA level, at the level of TE or TE-containing RNA transcripts, at the level of epigenetic modifications, or as a combination of any of these (Lanciano & Mirouze, 2018). Some prominent examples of stress-sensing mechanisms at different levels are:

- *A stress-related gene can become a hotspot for TE insertion*, as it is shown for a cold response gene and a TE from the roo family of transposons in Drosophila (Merenciano et al., 2016).
- TEs can cause *fast expansion of stress-related gene family* via retroduplication as in the hot pepper genome (Kim et al., 2017)
- TEs can *rewire entire regulatory networks of stress-related genes* as it is recently discovered for the role of ERVs in the immune response (Chuong et al., 2016), or the spreading of TF binding sites (Sundaram et al., 2014) or other cis-regulatory motifs (Ito et al., 2011) carried by TE sequences.
- TEs can make a locus stress-responsive by *changing the epigenetic landscape and consequently, the expression pattern* of nearby genes in response to stress (Galindo-González et al., 2017)
- *TE RNA can bind to complementary mRNA sequences of stress-related genes* and change their expression level as is shown for B2 TE RNA in mouse (Zovoilis et al., 2016).

As these and many other examples show, TEs activity as stress sensors is diverse and ancient; it exists in almost all species. On the other hand, the piRNA/PIWI system is restricted to multicellular animals. Nevertheless, it has become a crucial player in transposon control and adoption. First, PIWI/piRNAs not only keep the integrity of germline genomes in normal and stress conditions (Castañeda et al., 2011; Pappalardo et al., 2021) but also can modify the content and activity of the entire TE population at a genome-scale in evolution (Schneider et al., 2021) as well as at the very beginning of the individual life cycle of an organism – in germline. This modulation of TE content and activity obviously includes the capacities for stress response of the TE families in a genome.

Second, recently revealed important mechanisms of stress response relate to the interplay between piRNAs/PIWI proteins and TEs. Various stress-inducible effector proteins mediate such relationships. Two important examples are HSP70/HSP90 stress response in Drosophila and other animals and p53 mediated stress response in animals and human.

The HSP70 chaperone as a stress-responsive switch of piRNA/PIWI and TE activity

A recent study (Cappucci et al., 2019) reveals that heat shock response in Drosophila ovaries and testes is mediated by a system of chaperones and co-chaperones. At normal conditions, TEs are repressed by a piRNA-dependent mechanism mediated by the Hsc70/Hsp90 chaperone machinery which aids the loading of piRNAs onto Ago3 PIWI protein. After heat stress, significant activation of TEs is observed. Further analyses revealed that under heat shock the Hsc70/Hsp90 chaperone complex is reassigned from its normal functions in piRNA biogenesis and is recruited to deal with the general effects of heat stress. As a result, important protein factors of piRNA biogenesis are displaced to the lysosomes, piRNA biogenesis is disrupted, and massive de-repression of TEs is observed.

The stress-inducible chaperone Hsp70 is deeply conserved, its homologs exist in all kingdoms from bacteria to humans. It can be activated by many types of biotic and abiotic stress (Yu et al., 2015; Specchia & Bozzetti, 2021). So this mechanism may have broader evolutionary implications (Cappuchi et al., 2019). Under severe stress caused by rapid environmental changes, the switches in Hsp70 activity could aid the individuals' survival, but could also provoke a TE-mediated increase in the frequency of mutations in the germ cells, which, in turn, can raise the level of genetic variation, adaptability and evolvability in populations and species under stress (Gangaraju et al., 2011; Piacentini et al., 2014, Specchia & Bozzetti, 2021).

The tumor suppressor p53, TEs, and piRNA biogenesis

The prominent tumor suppressor and key transcription factor protein p53 (TP53 in human) is one of the most studied proteins in recent decades. It is known to regulate cell metabolism, proliferation, senescence, and apoptosis (Gudkov et al., 2011; Puzio-Kuter, 2011; Aubrey et al., 2016; Voskarides & Giannopoulou, 2023, among over 80000 studies on this most studied protein). The p53 protein is conserved across vertebrates and some invertebrates. In recent decades, important discoveries relate to p53 and TEs. Many p53 binding sites are reported to exist in the sequences of various primate-specific transposable elements: in LTR retrotransposons (Wang, T. et al., 2007), in Alu elements (Cui et al., 2011), and LINEs (Harris et al., 2009). The TEs binding motifs could have enriched significantly the evolution of p53 regulatory pathways based on the networking properties of TEs (Feschotte, 2008).

On the other hand, recent studies reveal important roles for p53 also in the control of TEs (Wylie et al., 2016a; Pitolli et al., 2019). Especially, activation of LINE retrotransposons can provoke p53 activity, and some p53-related cancers can be provoked by abnormal activity of retroelements caused by p53 inactivation (Tiwari et al., 2018; Tiwari et al., 2020). Interactions between p53 and components of the PIWI/piRNA pathway were also detected (Wylie et al., 2016a, 2016b), suggesting that p53 might collaborate with the PIWI/piRNA system to control the activity of retrotransposons. As reported from studies on Drosophila, p53 interacts with a key catalytic component of the piRNA network, Aubergine (Siomi et al., 2011). Moreover, loss of p53 causes abnormal accumulation of piRNA precursor RNAs, suggesting that p53 is important at certain steps of the piRNA biogenesis (Wylie et al., 2016a).

The complex interplay between p53, TEs, and PIWI/piRNA regulation emerges as a new level of regulatory complexity in the evolution of stress response in primates and human.

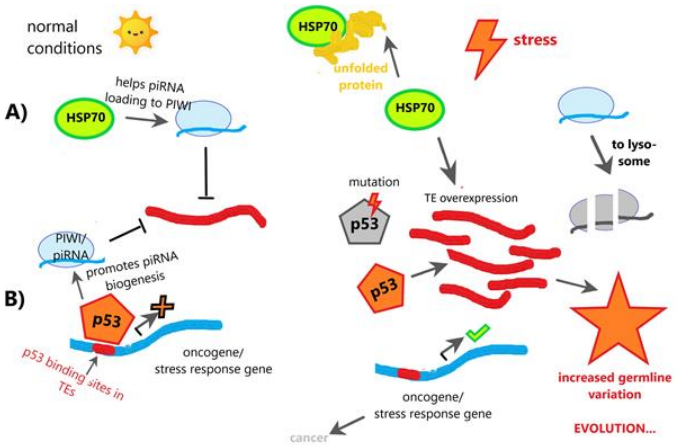

Figure 2. *PIWI/piRNAs, TEs, and stress responces.*
A simplified scheme of two stress response pathways involving TEs, PIWI/piRNAs and stress-inducible proteins. Various co-chaperones and co-factors are not shown.

A) In normal conditions, the stress-inducible chaperone HSP70 promotes piRNA loading onto PIWI proteins. piRNA silencing works properly and TEs are silenced. In stress conditions, HSP70 is recruited to fight with stress consequences (misfolded proteins), piRNA loading is hindered, PIWI proteins are directed to lysosome for degradation and TEs are out of control. In broader perspective, this could lead to increased inherited variation, and accelerated evolution of new traits.

B) Tumor suppressor p53 is a negative regulator of gene expression of hundreds important genes involved in cell proliferation, metabolism and signaling. Many p53 binding sites are in TE sequences inserted in promoter regions of various genes. Also, p53 is involved in piRNA precursor maturation. In normal conditions, p53 represses transcription of its targets and promotes piRNA biogenesis. In stress conditions (as in case of p53 mutation) p53 responds to TE overexpression and its function is disturbed. piRNA biogenesis is disrupted and TEs are out of control. This could lead to cancer and other disorders (transposopaties), but could also accelerate adaptation.

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Taken together, these observations imply a complex and multi-level role of piRNAs control over TEs and TE inducibility under stress, as well as far-reaching evolutionary implications (Figure 2).

Conclusions and perspective

PIWI/piRNA system components are key factors for genome integrity. They build functional links between protein-coding genes, transposons, and other genome components and form a complex genome-scale regulatory network that unifies the genome at the post-transcriptional level (Watanabe et al., 2015; Wang & Lin, 2021). In this respect, important features of organisms' reproduction, stress response and homeostasis, survival, development, and evolution could have been shaped in the course of the co-evolution between TEs and the PIWI/piRNA system.

Perhaps the most important conditions for evolution are germline development and reproduction, which pass on life and biological information through time, as well as stress sensing, stress responsiveness, and adaptation. Intriguingly, these two fields are also the most important arena of interactions between transposons and PIWI/piRNA system. The latter could be considered as a mediator between TEs and genome, balancing between fine-tuned regulation of beneficial, exapted TEs and silencing of dangerous TEs. In keeping this balance, the PIWI/piRNA system acts as an interpreter (reader) or adaptor of TE-encoded information (constructive or destructive).

As well as piRNA-based regulation is often redundant with other TE regulatory mechanisms (Rojas-Ríos & Simonelig, 2018), it could play also the role of an experimental system for testing novel opportunities for mRNA regulation and new biological functions, based on the interactions between piRNA and TE sequences at local and global scale.

Such "experimental" capacity of the PIWI/piRNA system could have been promoted also by the rapid evolution of piRNA clusters and the targeting properties of piRNAs, with important consequences on speciation, adaptation, and generation of novelties in the course of evolution.

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