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HYPOTHESIS

Transposon control as a checkpoint for tissue regeneration

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ABSTRACT

Tissue regeneration requires precise temporal control of cellular processes such as inflammatory signaling, chromatin remodeling and proliferation. The combination of these processes forms a unique microenvironment permissive to the expression, and potential mobilization of, transposable elements (TEs). Here, we develop the hypothesis that TE activation creates a barrier to tissue repair that must be overcome to achieve successful regeneration. We discuss how uncontrolled TE activity may impede tissue restoration and review mechanisms by which TE activity may be controlled during regeneration. We posit that the diversification and co-evolution of TEs and host control mechanisms may contribute to the wide variation in regenerative competency across tissues and species.

KEY WORDS: Transposable elements, Regenerative biology, Inflammation, Proliferation, Stem cells

Introduction

The discovery of transposable elements (TEs, also referred to as transposons) by Barbara McClintock in the mid-20th century was a turning point in our understanding of genetic variation (McClintock, 1950). TEs have been identified in all major branches of the tree of life (González-Delgado et al., 2021; Wells and Feschotte, 2020) and in nearly all sequenced eukaryotic genomes (reviewed by Wells and Feschotte, 2020). In many eukaryotes, including most metazoans, TEs comprise a large fraction of the nuclear genome. For example, about half of the human genome is composed of TEs (Hoyt et al., 2022). Animals with exceptionally large genomes, such as salamanders or lungfish, harbor even greater quantities of TEs, but species with small genomes may still contain a large fraction of TEs. *Drosophila* has one of the smallest insect genomes, but about one-fifth is composed of TEs (Mérel et al., 2020). We return to interspecies TE variation later in this Hypothesis, because we believe it holds a key to understanding why organisms differ in their regenerative capacity.

Despite their predominance in genomes, TEs have remained understudied relative to (host) genes for practical, technical and dogmatic reasons; their repetitive nature, high copy numbers and insertional polymorphisms create unique challenges for the study of TE biology. These same characteristics also stoke the mutagenic potential of TEs. *De novo* transposition events account for ∼50% and 10% of all spontaneous mutations in lab stocks of *Drosophila* (Eickbush and Furano, 2002) and mice (Kazazian and Moran, 1998), respectively. Over 100 human genetic diseases are the direct result of *de novo* transposition events (Kazazian and Moran, 2017; Payer and Burns, 2019). Additionally, the overproduction of TE products (nucleic acids and/or proteins) has been implicated in an increasing array of pathologies and homeostatic dysregulation, including cancers, autoimmune diseases, neurodegeneration and aging (Burns, 2020; Dubnau, 2018; Gorbunova et al., 2021; Küry et al., 2018; Tam et al., 2019). Clearly, TE dysregulation and uncontrolled propagation pose a threat to genome integrity and cellular homeostasis.

TEs and their hosts have evolved ways of mitigating the deleterious effects of transposition. Many TEs display 'behaviors' that minimize their activity and damaging effects while maximizing their propagation, such as self-regulatory mechanisms and insertion site preferences, making them less likely to disrupt gene function (Cosby et al., 2019; Lampe et al., 1998; Lohe and Hartl, 1996; Saha et al., 2015; Sultana et al., 2017). In parallel, hosts have evolved multiple mechanisms of TE control. Some are those used in gene regulation, but others target and repress TE activity more specifically. The latter are mediated by small RNAs (sRNA) or Krüppel-associated box-containing zinc-finger proteins (KRAB-ZFPs), which are discussed below and in several reviews (Bruno et al., 2019; Cosby et al., 2019; Ecco et al., 2017; Onishi et al., 2021; Ozata et al., 2019).

The continuous balancing of evolutionary adaptations between TEs and their hosts has culminated into a self-propagating arms race (McLaughlin and Malik, 2017). One hallmark of such an arms race is the rapid, continuous diversification of both host and TE arsenals. This is illustrated by the extensive diversification of sRNA pathways in certain clades of animals (e.g. worms) (Buck and Blaxter, 2013; Lewis et al., 2018), the adaptive evolution of protein-coding repressors (e.g. KRAB-ZFPs in tetrapods) (Emerson and Thomas, 2009; Jacobs et al., 2014), as well as evidence of escape and counter-defense strategies adopted by some TEs (Cosby et al., 2019; Hosaka et al., 2017). While these mechanisms are best understood in the context of the germline, some also operate in somatic tissues.

The biological impact of TEs is not limited to the time in which they are transpositionally active but extends long after they have spread and attained fixation within the population. First, their multiplication within a genome creates substrates for chromosomal rearrangement through non-allelic recombination events. This process is responsible for the duplication, deletion and rearrangement of vast amounts of DNA, including genes, over long evolutionary timeframes (Ade et al., 2013; Cerbin and Jiang, 2018; Han et al., 2008; Klein and O'Neill, 2018). Second, TEs often contain complex regulatory sequences that control the precise expression of their own coding and noncoding gene products that facilitate their mobilization (e.g. transposases). These regulatory sequences retain latent activities long after a TE has integrated into the genome and have the potential to influence a myriad of cellular processes, including host gene regulation and chromatin architecture (Chuong et al., 2017; Fueyo et al., 2022). Finally, parts of TEs may be captured to assemble evolutionarily novel protein-coding sequences serving organismal function (Bourque et al., 2018; Cosby et al., 2021; Jangam et al., 2017; Liu et al., 2021; Senft and Macfarlan, 2021). Through these and other processes, TEs have

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Box 1. TE classification

There are two classes of TEs: class I elements or retroelements transpose via a RNA intermediate that is reverse transcribed into a DNA copy that is integrated in the genome, while class II elements or DNA transposons are mobilized via DNA intermediates. TEs can be further divided into subclasses, superfamilies, families and subfamilies based on the method of genomic integration, sequence structure and size. For example, class I elements include elements with long terminal repeats (LTRs), such as endogenous retroviruses (ERVs) and elements without a LTR. The latter are further divided into short and long interspersed elements (SINEs and LINEs, respectively). TEs are exceptionally diverse, and their demographics and abundance vary extensively across organisms such that each species has a unique TE landscape. The table highlights a subset of TE types and families mentioned in the main text. For a more thorough review of TE classification and modes of transposition, see Wells and Feschotte (2020).

TE classification and select TE families

Class	Subclass	Superfamily	Family/subfamily examples	Species
Class I (retrotransposons)	Non-LTR	LINE	LINE1	*Homo sapiens*, *Mus musculus*
			L1Hs	*Homo sapiens*
		SINE	Alu	*Homo sapiens*
			B1	*Mus musculus*
	LTR	ERV	HERVH	*Homo sapiens*
			MERVL	*Mus musculus*
			RLTR10	*Mus musculus*
			IAPez	*Mus musculus*
Class II (DNA transposons)	DD(E/D) integrase	Tc1/mariner	Tc1	*Caenorhabditis elegans*
			Mos1	*Drosophila mauritiana*
		P	P element	*Drosophila melanogaster*

profoundly shaped genome function and evolution. The widespread integration of these elements into all manner of hosts and cellular processes is equally matched by their functional diversity. TEs are highly complex: diverse in prevalence, type, size and mode of transposition (Box 1), such that no two genomes – whether comparing within or across species – contain the same TE content (Bourgeois and Boissinot, 2019; Wells and Feschotte, 2020).

In this Hypothesis, we weave together findings and concepts from the seemingly unrelated regeneration and TE fields to stimulate future investigations into the impact and control of TE activity during tissue regeneration. We propose a model in which successful regeneration is dependent upon the ability of an organism to control TEs. We build the case that regenerating tissues create a cellular environment permissive to TE activity. We postulate that this introduces a checkpoint during tissue regeneration upon which TEs must be repressed for successful regeneration to occur. We outline key pathways involved in TE control and highlight known connections to tissue regeneration. We discuss how the co-evolution of TEs and their controllers has led to the divergence of TE landscapes and regulatory pathways across animal lineages, which may contribute to species- and/or tissue-specific variations in regenerative competency. Last, we discuss some of the challenges and limitations of our model. In this regard, it is important to note that most information regarding TE biology in animals is drawn from studies in humans, mice and *Drosophila*, rather than more regeneratively competent organisms. We acknowledge this limitation in our hypothesis, as there are many nuances and complexities to regeneration that we cannot fully address here.

Tissue regeneration

Tissue regeneration is the process through which an organism repairs trauma or injury. Across known injury models, common processes have emerged, specifically the temporal control of inflammatory signaling, dynamic chromatin remodeling, cellular proliferation and gene expression changes. From this, the regeneration timeline can be loosely condensed into three phases: (1) wound signaling; (2) stem/progenitor cell (SC) activation and clonal expansion; and (3) cellular differentiation and morphogenesis (Fig. 1) (Tiozzo and Copley, 2015). Briefly, wound signaling encompasses the release of inflammatory factors into the tissue microenvironment, which recruits myeloid cells to the injury site and activates resident SCs (initiating phase II). Once activated, SCs undergo dramatic chromatin landscape changes and re-enter the cell cycle. This phase is denoted by high levels of SC proliferation to produce nascent daughter cells and the gradual tempering of inflammation. Finally, in phase III, daughter cells undergo cell-specific differentiation programs and establish functional connections with existing tissues.

Although these generalized processes are observed in a broad range of species and injury models, regeneration competency is highly variable across eukaryotes. Organisms such as tunicates and planarians are capable of whole-body regeneration, whereas others, such as *Drosophila* and humans, display limited regenerative abilities and can regenerate only a subset of tissues (Srivastava, 2021). For example, retinal injury produces a similar inflammatory response in both mice and zebrafish; however, mice fail to produce new retinal neurons, whereas zebrafish do (Conedera et al., 2021). Moreover, within a given species, there is great variation in tissue-specific regeneration competency. In humans, skin and gastrointestinal tract tissues experience high cellular turnover and can quickly repopulate lost tissue, but this ability is not inherent across all tissues (Wells and Watt, 2018). Multiple intrinsic (genetic) and extrinsic (environmental) factors likely contribute to this inter- and intra-species variability, such as the availability of tissue-specific SCs or differential conservation of regeneration-responsive enhancers across species (Bowman and Trompouki, 2021; Garg et al., 2022; Goldman and Poss, 2020; Lai and Aboobaker, 2018). We argue that the differential activity and control of TEs across species and tissues hold another clue toward unraveling the regeneration competency puzzle. The following sections outline how the cellular processes governing regeneration create a unique environmental niche that is conducive to TE activity.

Phase I: wound signaling

A hallmark of tissue injury is the release of inflammatory signaling factors and activation of innate immunity (Eming et al., 2017), which has been observed in multiple species (Bodó et al., 2021; Comish et al., 2020; Ferrario et al., 2018; Leach et al., 2021; Leigh

Development (2022) 149, dev191957. doi:10.1242/dev.191957

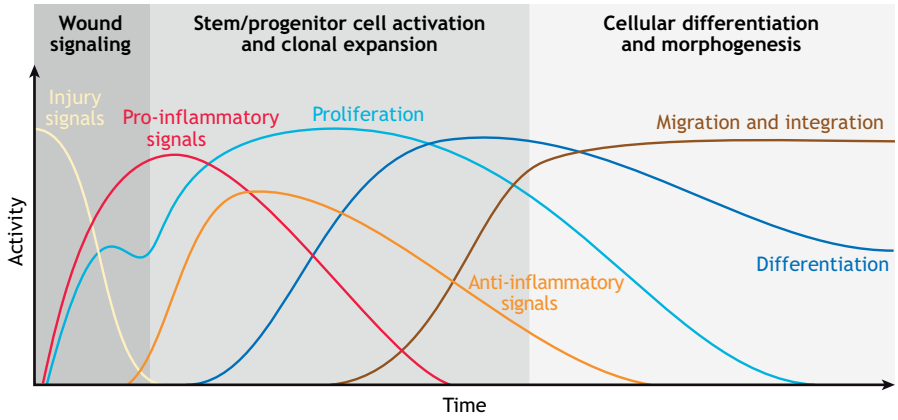

Fig. 1. Generalized timeline of known processes required for regeneration. Tissue regeneration can be broadly divided into three phases: wound signaling, stem/progenitor cell activation and clonal expansion, and cellular differentiation and morphogenesis. Phase I: wound signaling is characterized by the release of pro-inflammatory cytokines into the injured microenvironment. Phase II: pro-inflammatory signals trigger resident stem or progenitor cells (SCs) to exit quiescence and re-enter the cell cycle. SCs undergo rapid proliferation to repopulate lost tissues. Concurrently, pro-inflammatory signals decrease and anti-inflammatory signals increase. Phase III: inflammation and proliferation continue to decline as nascent daughter cells differentiate and integrate into existing healthy tissues, restoring functional cell-cell connections.

et al., 2018; Ren et al., 2020; Simkin et al., 2017; Swanson et al., 2020; Tsai et al., 2019; Tsarouchas et al., 2018; Wu et al., 2022). In vertebrates, tissue injury is characterized by the release of pro-inflammatory cytokines and interferons into the local microenvironment that attract myeloid cells to damaged tissues and signal to nearby SCs to exit cellular quiescence (Fig. 2, steps 1 and 2) (Hasegawa et al., 2017; Tsarouchas et al., 2018). After wound closure, the regenerative environment transitions to an anti-inflammatory state (Godwin et al., 2013; Hasegawa et al., 2017; Tsai et al., 2020). Importantly, the precise, temporal control of both pro- and anti-inflammatory signaling is crucial for regeneration, because either reduced or prolonged inflammation impedes tissue repair (King et al., 2012; Mescher et al., 2013; Tsarouchas et al., 2018). For example, inhibition of phagocyte recruitment blocked and/or stalled regeneration in salamanders (Godwin et al., 2013), frogs (Aztekin et al., 2020; King et al., 2012), zebrafish (Leach et al., 2021; Mathew et al., 2007; Silva et al., 2020; Tsarouchas et al., 2018), African spiny mice (Simkin et al., 2017) and tunicates (Rinkevich et al., 2007). These studies demonstrate that wound-induced inflammation is a conserved process across species and emphasize that inflammatory signaling must be tightly regulated to promote tissue regeneration.

TE activity is intricately linked to the innate immune system whether it is triggered by infection, injury or other cellular stressors (Gazquez-Gutierrez et al., 2021; Hale, 2022). Many long-terminal repeat (LTR) TE families harbor interferon-inducible enhancers and/or promoters within their sequences that can be bound by innate immunity transcription factors (TFs) (Fig. 2, steps 2′ and 3) to regulate expression of the TEs themselves (Gonzalez-Hernandez et al., 2012; Manghera et al., 2016) or nearby host genes (Chuong et al., 2016; Manghera et al., 2016; Srinivasachar Badarinarayan et al., 2020). Furthermore, TE-derived products, including double-stranded RNA (dsRNA), cDNA and proteins, activate host cell innate immunity when bound by antiviral sensors (Fig. 2, steps 4-7) (Gazquez-Gutierrez et al., 2021). For example, elevated levels of cytosolic LINE1 (Box 1) cDNA in human and rodent cells promoted interferon signaling when recognized by proteins of the cGAS-STING pathway (De Cecco et al., 2019; Gamdzyk et al., 2020; Simon et al., 2019). Furthermore, some TE transcripts form dsRNAs through inter- or intramolecular pairings recognized by the cytoplasmic antiviral proteins RIG-I, MDA-5 and ZBP1, and instigate an innate immune response (Ahmad et al., 2018; Lefkopoulos et al., 2020; Wang et al., 2020). These examples underscore an intimate interconnectedness between TEs and host immunity. Within the context of regeneration, this interplay could trigger a positive-feedback loop (Fig. 2, step 8) that, if left unchecked, would prolong inflammatory signaling within the wound microenvironment and create a barrier to tissue regeneration.

Phase II: stem/progenitor cell activation and clonal expansion

SCs driving tissue repair can arise from very different cellular lineages depending on species and tissue type, which also determines their potency (Blanpain and Fuchs, 2014; Ricci and Srivastava, 2018; Tiozzo and Copley, 2015); yet common processes exist in their injury response. After wounding, the release of inflammatory signals trigger resident or neighboring SCs to exit quiescence and re-enter the cell cycle (Fig. 2, steps 1-2′) (Iribarne, 2021; Mosteiro et al., 2016). Inflammation-induced SC activation was initially reported in *Drosophila* (Ryoo et al., 2004) and has since been identified in other injury models, including the zebrafish (Kyritsis et al., 2012; Nelson et al., 2013) and mouse (Han et al., 2015; Mosteiro et al., 2016; Nelson et al., 2015). Importantly, injury-induced inflammatory molecules were both necessary and sufficient to drive progenitor cell proliferation in the zebrafish brain (Kyritsis et al., 2012) and neonatal mouse hearts (Han et al., 2015). Knockout of pro-inflammatory genes *Tnfr1* or *Il6* impaired hepatocyte proliferation after liver injury in mice (Cressman et al., 1996; James et al., 2003, 2005), which emphasized the importance of immune signaling in SC activation. Once activated, SCs undergo extensive genome-wide changes in chromatin accessibility and gene expression (Gehrke et al., 2019; Goldman and Poss, 2020; Hoang et al., 2020; Murad et al., 2021; Zhang et al., 2021), which occurs within minutes to hours after injury. These changes allow for SC asymmetric cell division to promote self-renewal and produce a highly proliferative daughter cell (Gurevich et al., 2016; Lei et al., 2016; Nagashima et al., 2013; Vertii et al., 2018; Yang et al., 2017a). Compared with the parent SC, the daughter cell is characterized by an accelerated cell cycle for rapid production of nascent tissue (Egger et al., 2009; Ricci and Srivastava, 2018; Rost et al., 2016; Wenemoser and Reddien, 2010). Below, we outline

Development (2022) 149, dev191957. doi:10.1242/dev.191957

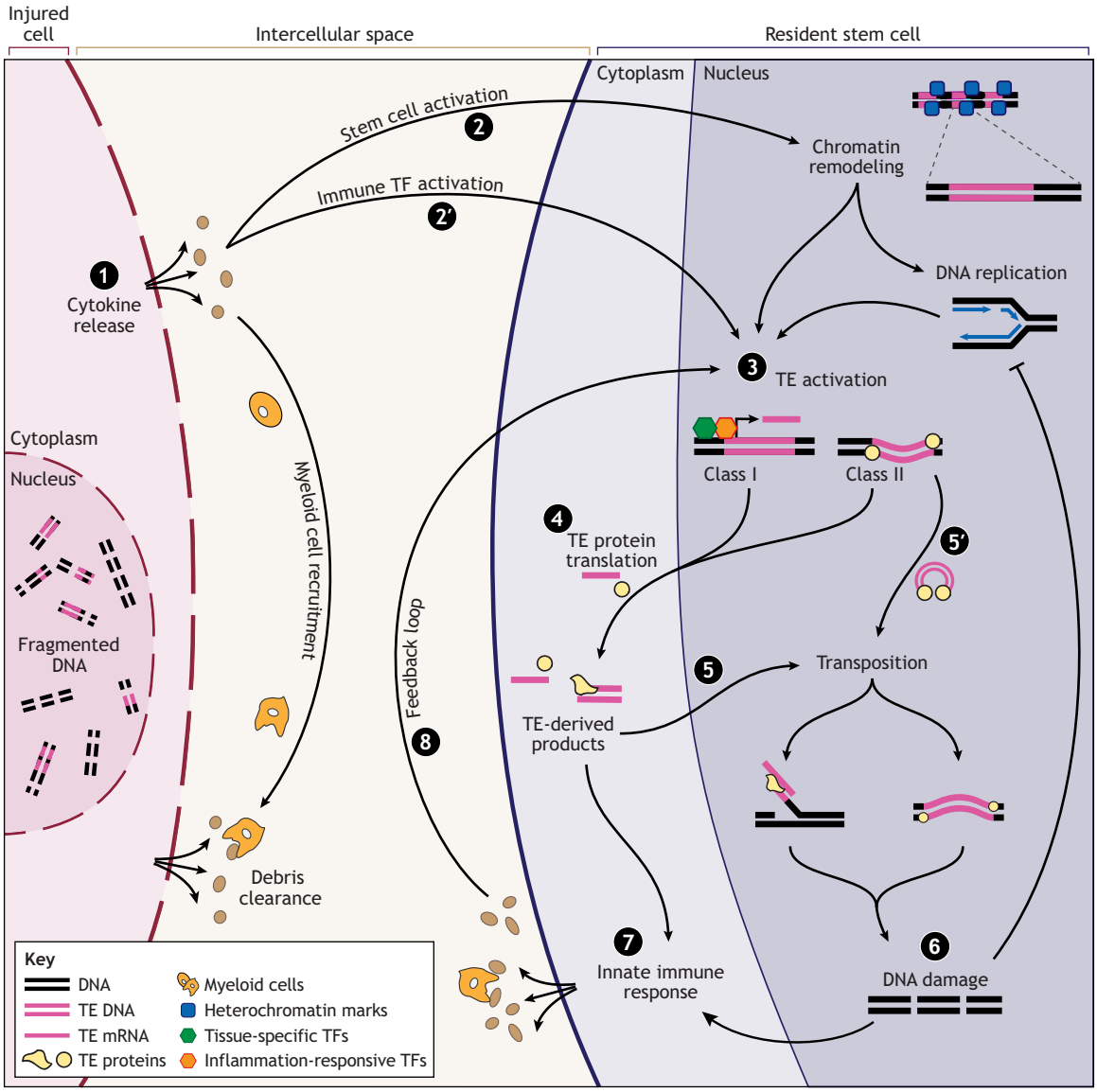

Fig. 2. The regeneration environment is conducive to transposable element (TE) activity. (1) Injury-induced signals are released from dying cells that recruit leukocytes to the injury site. (2) Inflammatory signals induce resident stem cell activation, resulting in changes to chromatin accessibility and gene expression. (2′) Inflammatory signals trigger immune-specific transcription factors to bind TE promoters. (3) TEs 'sense' the dynamic cellular environment and begin to be expressed and/or activated. (4) TE mRNA translocates to the cytoplasm for translation and/or reverse transcription (RT). (5) Class I products re-enter the nucleus and 'copy' themselves into a new genomic locus, whereas (5′) Class II products re-enter the nucleus and 'cut and paste' into a new locus. (6) Transposition results in DNA damage, which inhibits DNA replication. (7) TE-encoded products and DNA damage signals activate the host intracellular innate immune response. (8) TE-induced inflammation could propagate an inflammatory feedback loop.

how TEs may contribute to and use these proliferative environments for their propagation.

Do transposons mediate stem cell activation?

A limited but growing number of transcriptomic studies have reported increased TE expression after injury, particularly LTRs and LINEs, in regeneratively competent model organisms, including salamanders (Elewa et al., 2017; Zhu et al., 2012a), sea cucumbers (Mashanov et al., 2012), brittle stars (Mashanov et al., 2020) and earthworms (Shao et al., 2020); however, these studies were descriptive in nature and did not directly assess TE function or activity. Recently, genomic profiling of TE and gene expression after chemotherapy in mice revealed broad changes to chromatin accessibility and upregulation of DNA, ERV and LINE1 family expression within newly accessible loci (Clapes et al., 2021). Additionally, TE-derived dsRNAs were upregulated after gamma irradiation or chemotherapeutic injury in mouse (Clapes et al., 2021) and human (Mikhalkevich et al., 2021) myeloid cells, respectively, and interferon pathway induction was directly attributable to MDA5-bound TE dsRNAs in both models. Experimental overexpression of ERV and LINE1 dsRNAs led to hematopoietic SC activation and cycling, whereas knockdown of young LINE1 transcripts favored SC quiescence. Importantly, these SC responses were dependent upon MDA5-mediated inflammatory signaling (Clapes et al., 2021). Similar findings have been reported in other injury models that demonstrated a requirement for dsRNAs to promote interferon signaling, SC proliferation and regeneration (Kim et al., 2019; Lan et al., 2022; Nelson et al., 2015); however, these studies did not evaluate TE expression or activity. Together, these data provide evidence that TEs are upregulated after injury

Development (2022) 149, dev191957. doi:10.1242/dev.191957

across multiple model organisms and suggest that TEs may function as mediators of SC activation after injury.

Transposons manipulate and exploit stemness

TE expression and regulatory dynamics are tightly interwoven into the pluripotency status of a cell. For example, MERVL (Box 1) is a marker of totipotency in early mouse embryos, and its expression is sufficient to induce the two-cell state (Macfarlan et al., 2012; Yang et al., 2020). To transition into the pluripotent embryonic SC (ESC) state, MERVL transcription had to be downregulated, which was facilitated by upregulation and nuclear localization of LINE1 RNAs (Percharde et al., 2018). Additionally, *in vitro* reprogramming of mouse fibroblasts into an induced pluripotent SC (iPSC) state led to increased TE transcript and protein levels (e.g. LINE1, MERVL and IAPez) (Box 1) (Friedli et al., 2014; Macfarlan et al., 2012; Walter et al., 2016). In human ESCs, maintenance of ESC identity and gene expression was regulated by OCT4-bound HERVH (Box 1) transcripts (Lu et al., 2014; Wang et al., 2014), and the reprogramming of human fibroblasts into an iPSC state was sufficient to induce HERV expression (Friedli et al., 2014) and LINE1 transposition (Klawitter et al., 2016; Wissing et al., 2012). Importantly, TE expression is often driven by pluripotency-related TFs. Indeed, KLF4, OCT4, NANOG and SOX2, bind and promote HERVH transcription in human pluripotent cells *in vitro* (Carter et al., 2022; Göke et al., 2015; Lu et al., 2014; Ohnuki et al., 2014; Wang et al., 2014).

Beyond mammals, very little is known about TE activity in SCs. However, a recent report has found that LINE and LTR TEs actively transposed within *Drosophila* intestinal progenitor cells (Siudeja et al., 2021). Additionally, it has been reported that genomic LINE1 copy numbers increase (determined via DNA quantitative polymerase chain reaction) after repeated limb amputations in the axolotl (Zhu et al., 2012a). Despite our limited knowledge, these examples highlight how some TEs have adapted to capitalize on naïve cellular states to facilitate their genomic propagation. Future studies are needed to establish whether TEs influence 'stemness' outside the mammalian lineage and whether these regulatory interactions are important for regeneration.

Phase III: cell differentiation and morphogenesis

During the final phase of regeneration, newly generated daughter cells must acquire the proper cellular identity, migrate and form functional connections within the remaining healthy tissues. These processes correlate with nascent tissue maturation and the gradual decrease in inflammatory and proliferative expression dynamics, thereby returning to a pre-injury-like state. Interestingly, TE expression followed a similar trend during salamander limb regeneration, first increasing but resolving to near control levels by 7 days post-amputation (Elewa et al., 2017), indicating that TE expression is dynamic during regeneration.

Cell fate acquisition and tissue patterning during regeneration rely on the deployment of cell type-specific transcriptional networks that replicate, at least in part, programs used during embryogenesis (Goldman and Poss, 2020; Johnston et al., 2021 preprint; Soubigou et al., 2020). The same programs are also likely to regulate TE expression. Indeed, TE families often display highly specific expression patterns during embryonic development. For example, a recent transcriptomic study characterized TE family expression throughout early zebrafish development and found that TEs are expressed dynamically over time and in a cell type- and tissue-specific manner (Chang et al., 2022). Similar patterns were also described during murine (He et al., 2021; Shao and Wang, 2020) and sea urchin embryogenesis (Panyushev et al., 2021). Additionally, it is becoming increasingly evident that the specificity of TE expression found during early development may be controlled by tissue-specific TFs (Bourque et al., 2008; Chuong et al., 2013, 2016; Sundaram et al., 2014, 2017). For example, in human cells *in vitro*, SOX11 bound to and activated L1HS (Box 1) expression during neuronal differentiation (Orqueda et al., 2018), and the well-known oncogene P53 directly repressed LINE1 transcription by binding its 5′UTR (Harris et al., 2009; Tiwari et al., 2020). For a more thorough review of TEs and their TF activators, see Hermant and Torres-Padilla (2021). These data indicate that TE expression is highly dynamic after injury and implicate host tissue-specific TFs as key regulators of TE expression during regeneration.

Transposon activity as a barrier to regeneration

Despite any potential benefits TEs may imbue on host regeneration, their dysregulation is more likely to impede regeneration than to promote it, often leading to increased mutagenesis and/or loss of cellular homeostasis. For example, TE dysregulation is increasingly recognized as an important facet of human cancers (Burns, 2017), which often have a similar environmental niche to that of a regenerating tissue [e.g. stemness, proliferation and inflammation (reviewed by Wong and Whited, 2020)]. In this section, we discuss the detrimental aspects of uncontrolled TE activity and highlight how TEs may be directly impeding mammalian regeneration.

Some cells cannot handle the (transposon) heat

Regeneration competency is dependent upon organismal age. Older tissues are marked by increased levels of inflammation- and senescence-related factors (Mogilenko et al., 2021). Generally, cellular senescence is defined as a stress response to intracellular and extracellular signals, such as cytokines (Hubackova et al., 2012), DNA damage (Micco et al., 2006) or excessive proliferation (Harley et al., 1990), resulting in cell cycle arrest and diminished tissue repair efficacy (Paramos-de-Carvalho et al., 2021a; Rhinn et al., 2019). Importantly, cellular senescence is also correlated with reduced heterochromatin (e.g. DNA methylation or H3K9me3), thereby relieving TEs from repression (De Cecco et al., 2013, 2019; Dubnau, 2018; Gorbunova et al., 2021; Van Meter et al., 2014; Simon et al., 2019). TE loci are generally enriched for repressive chromatin marks to maintain their suppression (Deniz et al., 2019; Haggerty et al., 2021; He et al., 2019; Liu et al., 2018; Robbez-Masson et al., 2018; Rowe et al., 2010; Walsh et al., 1998), and when dysregulated under senescent conditions, accumulation of TE-derived products exacerbates senescence-related signaling and increases the likelihood of generating DNA double-strand breaks and age-related phenotypes, as reported in yeast (Maxwell et al., 2011), *C. elegans* (Dennis et al., 2012), *Drosophila* (Chang et al., 2019; Chen et al., 2016), mice (De Cecco et al., 2019; Van Meter et al., 2014; Simon et al., 2019) and human cells (De Cecco et al., 2013). For example, the accumulation of LINE1 and Alu (Box 1) RNA was sufficient to induce DNA damage and cellular senescence in human differentiated cells and SCs *in vitro* (Belancio et al., 2010; De Cecco et al., 2019; Wang et al., 2011). A similar mechanism was reported in aging *Drosophila* fat bodies, where TE upregulation resulted in increased DNA damage (Chen et al., 2016). Treatment of aged mice with reverse transcriptase inhibitors (RTI) successfully blocked TE activity and reduced DNA damage and inflammation (De Cecco et al., 2019; Simon et al., 2019).

Senescent cells have been found after injury in multiple animal models, including the salamander (Yun et al., 2015), zebrafish

Development (2022) 149, dev191957. doi:10.1242/dev.191957

(Paramos-de-Carvalho et al., 2021b; Da Silva-Álvarez et al., 2020) and mouse (Dookun et al., 2020; Dungan et al., 2022; Paramos-de-Carvalho et al., 2021b). Senescent cells actively secrete immunomodulatory factors that attract (or retain) phagocytes (Yun et al., 2015) and induce paracrine senescence in neighboring healthy cells (Acosta et al., 2013; Lehmann et al., 2022; Nelson et al., 2012; Yun et al., 2015). This feedforward inflammatory loop is a common feature of mammalian injury and is often accompanied by tissue fibrosis that impairs tissue restoration (Meyer et al., 2016; Paramos-de-Carvalho et al., 2021b; Schafer et al., 2017). For example, in a rat model of neurodegeneration, LINE1-derived cDNA and proteins accumulated in the cytoplasm of degenerating cortical neurons within 48 h of hypoxic-ischemic injury, and correlated with increased cGAS-STING activity and an expansion of the infarcted area (Gamdzyk et al., 2020). Further experiments revealed that RTI treatment attenuated cytoplasmic accumulation of LINE1 cDNA, decreased STING signaling and reduced the infarction spread (Gamdzyk et al., 2020). Recently, it was found that senescent cell ablation in injured mice attenuated tissue inflammation and improved functional recovery of cardiac, skeletal muscle and spinal cord tissues (Dookun et al., 2020; Dungan et al., 2022; Paramos-de-Carvalho et al., 2021b). By contrast, in models of successful regeneration, such as zebrafish, salamanders and even mouse skin, senescence-related signaling is only transiently upregulated after injury (Demaria et al., 2014; Paramos-de-Carvalho et al., 2021b; Da Silva-Álvarez et al., 2020; Yun et al., 2015), and elimination of senescent cells in these contexts, as in injured zebrafish fins (Da Silva-Álvarez et al., 2020), was sufficient to impair regeneration. When considered in the context of our model that the regeneration environment is conducive to TE activity, one might speculate whether TE activity is responsible for propagating senescent signaling in less regeneratively competent organisms and as a result directly contributes to fibrotic scar formation, further implying the need for measured and controlled senescent signaling during regeneration.

Transposition fractures replicating DNA

Many organisms use rapid SC proliferation to repopulate lost tissues; however, repeated cycling increases the risk of sustaining replication stress, which occurs when DNA polymerase has difficulty replicating repetitive regions of the genome (Barlow et al., 2013; Lyu et al., 2019) leading to DNA double-strand breaks (DSBs) and cell cycle exit (Técher and Pasero, 2021). For example, rapidly dividing human iPSCs become marred by DNA DSBs before exiting the cell cycle (Vallabhaneni et al., 2018). By contrast, regeneratively competent organisms mitigate DNA damage by employing a robust DNA damage response (DDR) to correct mutational errors and to retain SC viability and proliferative capacity (Lei et al., 2016; Sousounis et al., 2020). In axolotls, disruption of the DDR resulted in high levels of genotoxic stress, reduced proliferation and impaired limb regeneration (Sousounis et al., 2020), and similar results were also reported after knockdown of DDR genes (e.g. *p53* or *rad54b*) in injured planaria (Lei et al., 2016; Pearson and Sánchez Alvarado, 2009). Interestingly, mammalian SCs also upregulated the DDR pathway in response to injury and were able to maintain cell viability, but still underwent cell cycle arrest and could not successfully repair damaged tissue (Sotiropoulou et al., 2010).

Some TEs use key steps during cellular proliferation to mediate their transposition. For example, LINE1 TEs rely heavily on DNA replication for their mobilization (Fig. 2, step 5) (Ardeljan et al., 2020; Flasch et al., 2019). In human cells *in vitro*, LINE1 ribonucleoprotein complexes are translocated into the nucleus during mitosis, where they localize to DNA replication forks and interact directly with the pro-proliferative factors PCNA and MCM6 (Mita et al., 2018). Inhibition of the cell cycle using a chemical modulator successfully blocked retrotransposition in human cancer cells and was correlated with decreased LINE1 expression (Shi et al., 2006). These data suggest that, after injury, increased TE activity may underlie the accumulation of DNA damage in proliferating SCs, and in less regeneratively competent species this could lead to stalled regeneration.

Mechanisms of TE regulation during regeneration

The need for organisms to repress transposition is underscored by the fact that uncontrolled activity of a single TE family can have catastrophic consequences on organismal fitness. This is illustrated by the classic example of hybrid dysgenesis in *Drosophila*, which is triggered by germline mobilization of the P element (a DNA transposon) (Box 1) and causes sterility (Kidwell et al., 1977). The highly mutagenic activities of TEs have led to decades of research focused on unmasking how organisms control transposition (Bruno et al., 2019; Gutbrod and Martienssen, 2020; Rojas-Ríos and Simonelig, 2018; Schorn and Martienssen, 2018). Here, we discuss sRNA TE repression mechanisms, primarily focusing on the P-element induced wimpy testis (PIWI)-interacting RNA (piRNA) pathway, which is well characterized for its robust control of TEs in gonads and consider its potential function during tissue regeneration. We then briefly outline TE regulation in the context of other sRNA pathways and conclude with ZFPs, a non-sRNA, tetrapod-specific TE repression mechanism, all of which are less well studied but may play a pivotal role in restricting TEs during regeneration (Fig. 3).

piRNA pathway

The piRNA pathway is widespread among animals, originating early in metazoan evolution (Bagijn et al., 2012; Grimson et al., 2008; Houwing et al., 2007; Lewis et al., 2018; Lim et al., 2014), and is primarily known for its role in germline SC maintenance (Cox et al., 2000; Das et al., 2008; Deng and Lin, 2002; Houwing et al., 2007; Kuramochi-Miyagawa et al., 2004; Lin and Spradling, 1997) and TE repression (Aravin et al., 2007; Bagijn et al., 2012; Brennecke et al., 2007; Carmell et al., 2007; Houwing et al., 2007; Saito et al., 2006; Sarot et al., 2004). piRNAs often derive from piRNA clusters, which are genomic regions rich in TE sequences, to produce long single-stranded RNAs (Fig. 4A). Once transcribed, precursor RNAs are exported to the cytoplasm and associate with mitochondria before being processed into small mature piRNAs and possibly undergoing secondary amplification via the ‘Ping-Pong’ cycle. Once mature, piRNAs regulate TEs through either post-transcriptional gene silencing in the cytoplasm and/or transcriptional gene silencing within the nucleus. For more information regarding piRNA biogenesis and function, we refer our readers to more focused reviews (Iwasaki et al., 2015; Onishi et al., 2021; Ozata et al., 2019). The majority of PIWI and piRNA functional studies have been conducted in *Drosophila* (Brennecke et al., 2007; Dönertas et al., 2013; Onishi et al., 2021; Sienski et al., 2012; Thomas et al., 2013) and mouse gonads (Aravin et al., 2006, 2007; Ernst et al., 2017; Manakov et al., 2015; Newkirk et al., 2017; Onishi et al., 2021; Ozata et al., 2019). For example, in *Drosophila* ovaries, *Piwi* transcript levels are typically high; however, as ovaries age, *Piwi* expression gradually declines to result in increased transposition events, immune signaling and

Development (2022) 149, dev191957. doi:10.1242/dev.191957

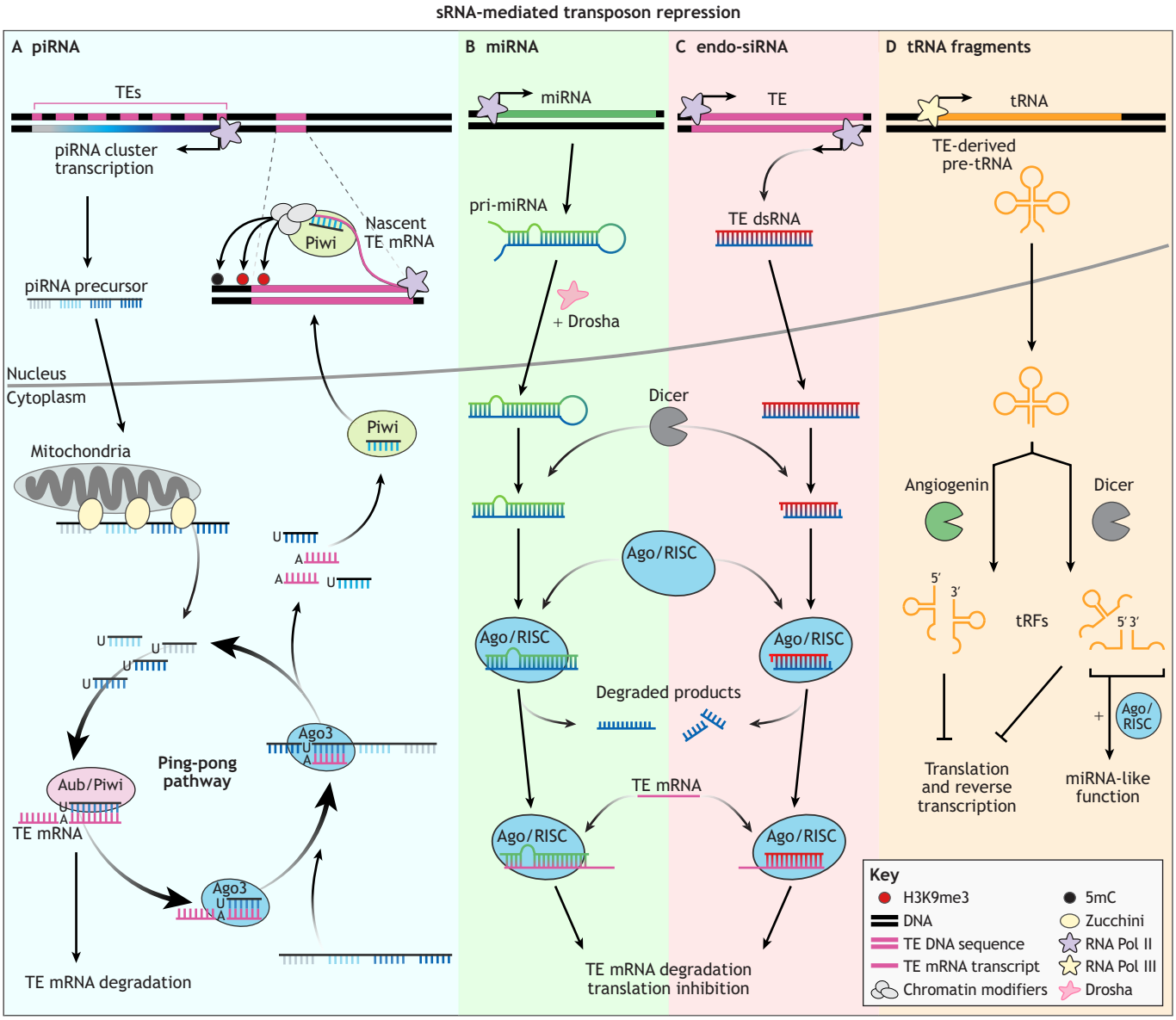

Fig. 3. Known small RNA (sRNA) pathways involved in transposable element (TE) repression. (A) piRNA pathway: piRNAs precursors are transcribed from piRNA clusters then translocate to the cytoplasm where they undergo processing and are amplified through the ping-pong pathway by Piwi pathway proteins (e.g. Aub, Piwi and Ago3). Once processed, piRNAs bind TE sequences via sequence complementarity to inhibit TE translation or translocate into the nucleus to inhibit TE transcription. (B) miRNA pathway: pri-miRNA precursors form dsRNA hairpin structures, and are tails are cleaved by Drosha before translocation from the nucleus. In the cytoplasm, double-stranded miRNAs are processed by Dicer and loaded into the Ago/RISC complex as single-stranded miRNAs that can then mediate TE mRNA degradation and translation inhibition. (C) Endo-siRNA pathway: endo-siRNAs can be generated from repetitive genomic loci, including TEs, and are processed by the same machinery as miRNAs. (D) tRNA fragments: tRNA fragments are generated from repeat tRNA loci. Once in the cytoplasm, pre-tRNAs are processed by Dicer or angiogenin, which cleave the tRNA at different nucleotide sites to produce tRNA fragments (tRFs). Once mature, tRFs regulate TE translation and reverse transcription. Pathways are modeled primarily from *Drosophila melanogaster* and *Mus musculus*. RISC, RNA-induced silencing complex.

the production of viral-like particles from an undetermined retrotransposon, ultimately leading to germline SC loss (Lin et al., 2020). Although the piRNA pathway is often considered to be germline-restricted, there is growing evidence indicating that the piRNA pathway may contribute to cellular homeostasis across a variety of somatic tissues (Funayama et al., 2010; Lewis et al., 2018; Rojas-Ríos and Simonelig, 2018).

Piwi proteins are highly expressed in neoblasts, an invertebrate-specific SC that contributes to tissue regeneration (Alié et al., 2011; Funayama et al., 2010; Juliano et al., 2014; De Mulder et al., 2009; Palakodeti et al., 2008; Reddien et al., 2005; Rinkevich et al., 2010; Shibata et al., 2016; Srivastava et al., 2014; Teefy et al., 2020; Zattara et al., 2016; Zavalnaya et al., 2020; Zhou et al., 2015). In animals capable of complex tissue regeneration (e.g. planarians and *Hydra*), Piwi proteins contribute to SC self-renewal (Juliano et al., 2014; De Mulder et al., 2009; Reddien et al., 2005; Shibata et al., 2016; Teefy et al., 2020; Zhou et al., 2015). Piwi-mediated SC self-renewal is also found in the *Drosophila* intestine (Sousa-Victor et al., 2017), indicating that Piwi proteins act as essential mediators of SC maintenance across animal lineages.

Development (2022) 149, dev191957. doi:10.1242/dev.191957

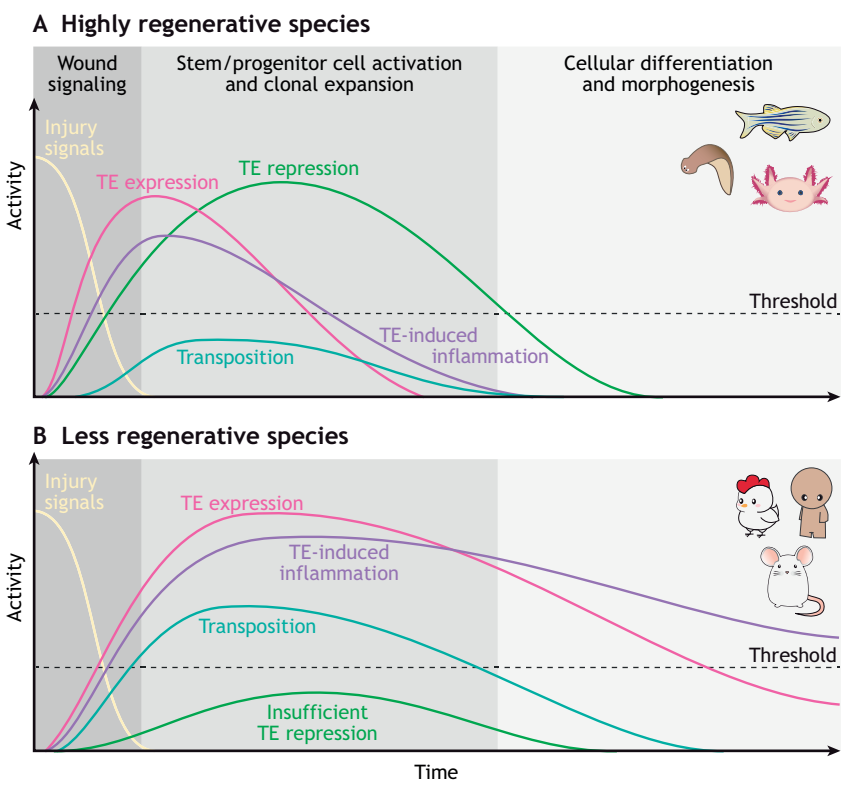

Fig. 4. Hypothesis: transposable element (TE) repression is required for tissue regeneration. TE expression (magenta) increases shortly after injury (yellow), which results in TE-induced inflammatory signaling (purple). TEs retaining functional DNA and protein-coding sequences will attempt to transpose (blue) and, given sufficient time, accumulation of TE mutagenic activity would bypass the host cell 'threshold' (dotted line), disrupting homeostasis and forcing the cell to enter senescence. In response, host cells must deploy TE repression mechanisms (green) to limit TE activity. (A) Regeneratively competent organisms (e.g. planarian, zebrafish and axolotl) effectively deploy TE countermeasures, thereby limited TE activity to below threshold levels and allowing for successful regeneration (gray). (B) Less regeneratively competent organisms (e.g. humans, chickens and mice) cannot effectively limit TE mutagenic events and incur too many cellular deficits, leading to regeneration stall.

As noted in the brain, intestine and fat body of *Drosophila*, Piwi proteins exert TE repressive activity in these tissues (Jones et al., 2016; Li et al., 2013; Perrat et al., 2013; Sousa-Victor et al., 2017). In mouse neural progenitor cells, knockdown of Mili (a Piwi homolog) leads to an increase in B1 SINE RNA (Box 1) transcripts, inflammation and senescence-related signaling (Gasperini et al., 2021 preprint), suggesting the TE repressive function of the Piwi pathway has been retained in some mammalian somatic tissues. In the planarian, *Dugesia japonica*, *Piwi* is not expressed by somatic cells; however, neoblasts deposit Piwi proteins into somatic daughter cells during cell division where they regulate TE activity and cellular differentiation (Shibata et al., 2016). In *Schmidtea mediterranea*, another planarian species, heterochromatin marks are maintained along TE loci by SMEDWI-2 (a PIWI homolog), and its knockdown leads to tissue-specific upregulation of diverse TE families and aberrant cellular differentiation (Li et al., 2021).

After injury, *Piwi* upregulation is detected within the invertebrate wound blastema (Kozin and Kostyuchenko, 2015; Rinkevich et al., 2010, 2013; Xu and Sun, 2020; Zhou et al., 2015) and is essential for tissue outgrowth (Rinkevich et al., 2010, 2013; Sousa-Victor et al., 2017; Srivastava et al., 2014). However, beyond planarian regeneration, very little is known about piRNA pathway function after injury. In the axolotl, *Piwil1* and *Piwil2* are upregulated in the limb blastema at 7 days post-amputation compared with controls (Zhu et al., 2012b), and morpholino knockdown of *Piwil1* and *Piwil2* decreases proliferation and increases apoptosis, which significantly impairs limb outgrowth out to 47 dpi (Zhu et al., 2012b). It should be noted that the timing of *Piwi* upregulation within the blastema correlates with the proliferation phase of regeneration (phase II), further implicating Piwi proteins in the regulation of SC proliferation and/or maintenance after injury. Recently, it has been determined that *Miwi* (the murine homolog of Piwi) mRNA and protein levels are downregulated within 4 days following mouse sciatic nerve transection and return to near control levels by 14 days post-injury (dpi) (Sohn et al., 2019). In this same study, piRNAs were differentially regulated at 7 dpi; however, Miwi levels remained downregulated at that timepoint (Sohn et al., 2019). Although TE activity was not assessed, the pattern of Miwi expression after injury is intriguing as it stands in stark contrast to the reported Piwi expression after injury in invertebrates and the axolotl.

Alternative mechanisms of TE control

Although there is mounting evidence that the piRNA pathway may be involved in TE silencing during regeneration in some metazoans, it is important to consider the role of other TE control pathways that may substitute or overlay the piRNA pathway.

MicroRNAs

The microRNA (miRNA) pathway (Fig. 4B) regulates key processes during regeneration, including SC proliferation and self-renewal (Kara et al., 2019; Tian et al., 2015), cellular differentiation (Cheng et al., 2009; Fordham et al., 2015; Makeyev et al., 2007), inflammation (O'Connell et al., 2007; Tili et al., 2007) and wound signaling (Das et al., 2014; Li et al., 2017; Wang et al., 2012), and although this pathway is a well-established mechanism of TE control in plants (Borges et al., 2018), it remains an understudied aspect of TE regulation in animals. However, *let*-7 and *miR-128* miRNAs bind LINE1 mRNAs and inhibit LINE1 transposition within human tumors and pluripotent SCs *in vitro* (Hamdorf et al., 2015; Tristán-Ramos et al., 2020), indicating that some miRNAs function to repress TEs in replicating cells.

RNA interference

Endogenous small interfering RNAs (endo-siRNAs) derive from long dsRNA precursors transcribed from TE and other repetitive

Development (2022) 149, dev191957. doi:10.1242/dev.191957

loci, which are processed by the RNase III enzyme Dicer (Ghildiyal et al., 2008; Okamura et al., 2008; Onishi et al., 2021; Russo et al., 2016). In *Drosophila*, mice and human cells, endo-siRNAs function in TE control (Babiarz et al., 2008; Chung et al., 2008; Ghildiyal et al., 2008; Kawamura et al., 2008; Okamura et al., 2008; Russo et al., 2016) (Fig. 4C). For example, in *Drosophila*, loss of an essential endo-siRNA pathway effector, *Ago2*, increased TE expression and transposition (Li et al., 2013; Russo et al., 2016). In mouse oocytes, loss of the endo-siRNA processing enzyme *Dicer* resulted in deficient endo-siRNA production and a fivefold upregulation of the RLTR10 (Box 1) family of endogenous retroviruses (Watanabe et al., 2008). Interestingly, upon global hypomethylation in mouse ESCs and primordial germ cells, the endo-siRNA pathway was upregulated in response to TE derepression, suggesting endo-siRNAs may function as 'emergency responders' to mediate TE control (Berrens et al., 2017). Moreover, in human cells, Dicer formed a complex with the dsRNA editing enzyme ADAR1 to process double-stranded Alu SINE transcripts into endo-siRNAs, which functioned to regulate gene expression and cellular apoptosis by binding the 3′ UTR of target transcripts (Shiromoto et al., 2020). Although endo-siRNA have not yet been examined during tissue regeneration, their presence in somatic tissues and diverse interactions with TEs make them prime candidates for TE control during regeneration.

tRNA-derived fragments (tRFs)

tRFs represent a recently identified mechanism of sRNA-mediated TE repression (Schorn and Martienssen, 2018) generated through endonucleolytic cleavage of tRNAs to produce 18-30 nucleotide long RNA fragments (Magee and Rigoutsos, 2020; Schorn and Martienssen, 2018) and function in a broad range of cellular processes (Schimmel, 2018; Su et al., 2020) (Fig. 4D). tRFs have not yet been functionally evaluated during regeneration, but two recent studies reported the differential regulation of tRFs during regeneration in planarians (Cao et al., 2020; Lakshmanan et al., 2021) with the peak of tRF expression occurring within the first 24 h post-injury (Cao et al., 2020). The combination of early tRF expression changes after injury with their novel role in TE repression makes tRFs important candidates for future exploration in the context of tissue regeneration.

Zinc-finger proteins

ZFPs bind DNA via their C2H2 zinc-finger motif in a sequence-specific manner (Urrutia, 2003). Many animal lineages have expanded their ZFP repertoire and there is evidence that in vertebrates this evolutionary pattern is correlated with and potentially driven by lineage-specific amplification of TEs (Bruno et al., 2019; Senft and Macfarlan, 2021; Thomas and Schneider, 2011). In tetrapods, the majority of ZFPs contain a KRAB domain, which forms a repression complex targeting TE loci (Ecco et al., 2016; Imbeault et al., 2017; Liu et al., 2018; Robbez-Masson et al., 2018; Yang et al., 2017b). Several KRAB-ZFPs recognize and silence specific TE families during early mouse and human embryonic development (Castro-Diaz et al., 2014; Jacobs et al., 2014; Rowe et al., 2010; Turelli et al., 2014; Wolf et al., 2015), and are expressed in a wide variety of tissues and developmental contexts (Bruno et al., 2019; Corsinotti et al., 2013; Cosby et al., 2019; Ecco et al., 2016; Imbeault et al., 2017; Playfoot et al., 2021). KRAB-ZFPs also function across a wide range of biological processes, including genome stability, epigenetic imprinting and SC self-renewal (Ecco et al., 2017; Senft and Macfarlan, 2021), supporting the possibility that KRAB-ZFPs may also function to repress TEs during regeneration.

Rapid evolution of TE control mechanisms

TE regulatory pathways are just as diverse as the TEs they regulate. A hallmark of these defense systems is their ability to adapt to the ever-changing TE populations that threaten genome integrity. For example, genes in the piRNA pathway are rapidly evolving alongside their TE targets (Lewis et al., 2016; Yi et al., 2014), and as components of the piRNA pathway diversify, their functions also diverge across species (Gutierrez et al., 2021; Lewis et al., 2018; Nishida et al., 2018; Wynant et al., 2017). TEs are similarly engaged in arms races with ZFPs (Bruno et al., 2019; Cosby et al., 2019; Thomas and Schneider, 2011; Yang et al., 2017b). First, the number of ZFP genes in vertebrate genomes is highly correlated with the abundance of retroelements (Thomas and Schneider, 2011). Second, some KRAB-ZFP genes have adapted to bind and repress specific, active TE families. The descendants of these TEs have, in turn, evolved to evade KRAB-ZFP targeting (Jacobs et al., 2014; Najafabadi et al., 2015; Wolf et al., 2020). Such co-evolutionary relationships signify an inter-dependency of TEs and their regulators, and it predicts that species with diverse, active TE landscapes must be endowed with dynamic and effective control systems. Alternatively, some TEs may have evaded host repression by developing commensal or mutualistic relationships (Cosby et al., 2019). Either possibility implies that species experiencing low TE activity have relaxed selective pressure to repress transposition in the germline, which causes the erosion, and eventual loss, of cellular control systems.

Perspectives and challenges

The observations summarized above suggest that controlled TE activity plays a significant role during tissue regeneration. First, tissue injury induces an inflammatory response that TEs respond to and propagate. Second, cycling progenitor cells undergo large-scale chromatin remodeling and regulatory reprogramming, which may release TEs from silencing mechanisms. Third, TE activity directly contributes to inflammation, DNA damage and cellular senescence, all of which must be precisely controlled for successful tissue repair (García–Lepe et al., 2022; Mescher et al., 2017; Walters and Yun, 2020). Fourth, tissue injury induces TE upregulation across a wide range of regeneration models, and this dysregulation, as reported in salamanders, was resolved upon trauma resolution (Elewa et al., 2017). Lastly, key effectors of TE regulation, such as Piwi proteins, are SC markers and required for regeneration in several organisms with high competency (Rinkevich et al., 2010, 2013; Shibata et al., 2016; Sousa-Victor et al., 2017; Srivastava et al., 2014; Zhu et al., 2012b). Collectively, these observations point to an intriguing relationship between TEs and tissue regeneration.

While it remains to be seen whether these findings are generalizable across a broad range of organisms and tissues, they suggest a model whereby controlled TE activity represents a checkpoint for regeneration. We propose that the rate at which TE sequences decay and lose activity, and the degree by which a host (or tissue) maintains the ability to control TEs, creates a balance that determines – in part – the ability of an organism (or tissue) to maintain their capacity for regeneration. As we have discussed, TEs are poised to be transcriptionally activated by injury. While their activation may initially facilitate the regeneration process by promoting inflammation (e.g. via nucleic acid-sensing and viral mimicry), these activities, if left unchecked, would severely impede regeneration. Thus, TE activation followed by repression creates a

Development (2022) 149, dev191957. doi:10.1242/dev.191957

'checkpoint' for regeneration. Species or tissues which deploy effective TE control strategies in response to the initial wave of TE activation upon injury can proceed with tissue repair; whereas species or tissues that do not, stall and are unable to properly regenerate (Fig. 4). This model predicts that species whose lineages have experienced the most TE activity often have retained greater regenerative capacities because they are better equipped to control TE reactivation.

This model makes specific predictions that can be tested experimentally using a rapidly expanding toolkit to manipulate TE activity. For example, targeted epigenetic manipulations, such as CRISPR-inhibition or -activation, are powerful tools to manipulate large sets of TEs or their control systems (Fuentes et al., 2018; Fueyo et al., 2022). Furthermore, small molecule inhibitors, such as RTIs and integrase inhibitors (to prevent the formation of cDNA or transposition, respectively), can be used to block the generation of transposition intermediates or chromosomal integration (Das et al., 2016; Marchand et al., 2007; Thomas et al., 2017). Antisense-locked nucleic acids are also effective at targeting specific TE RNAs for degradation (Percharde et al., 2018), and TE regulatory pathways are well-suited for genetic (Coluccio et al., 2018; Houwing et al., 2007; Wood et al., 2016) or chemical (Aztekin et al., 2020; Brocks et al., 2017; Jorstad et al., 2017; Zhang et al., 2022) perturbations.

The studies reviewed herein provide an overview of TE expression dynamics and of the potential impact of TE activities throughout the regeneration timeline. However, these analyses are also complicated by technical hurdles that have limited previous investigations of TE activities in regeneration. For example, many studies have been conducted in highly regenerative organisms that do not yet have complete or well-annotated genome assemblies (Elewa et al., 2017; Mashanov et al., 2012, 2020; Shao et al., 2020; Zhu et al., 2012a), and most techniques used in these studies lack the genomic resolution required to infer the exact TE loci implicated. These limitations also hamper analysis in relation to neighboring genes, obscuring the mechanisms by which these elements are transcribed or regulated, or how they may affect host gene regulation. Lastly, it remains generally unclear whether the observed changes in TE activity from these studies directly impact – whether stimulating or opposing – the regenerative process.

Recent progress has been made toward the development of computational tools tailored for genomic analysis of TEs, alleviating some of their inherent difficulties. For example, methods have been developed to infer from RNA-seq data whether TEs are transcribed from their own promoters or from read-through transcription of host gene promoters (Lanciano and Cristofari, 2020). The continuous development of genomic technologies, including long-read sequencing (Amarasinghe et al., 2020; Berrens et al., 2021; Goerner-Potvin and Bourque, 2018; Jain et al., 2016; Rhoads and Au, 2015; Hoyt et al., 2022), is bound to further facilitate TE analysis and yield an increasingly unbiased and precise picture of their activities during regeneration. Furthermore, the expanding toolkit for the annotation, manipulation and functional characterization of TEs (Chu et al., 2021; Flynn et al., 2020; Fueyo et al., 2022; Negm et al., 2021; Storer et al., 2021) will help discern whether the response of TEs during regeneration is merely a byproduct or directly impacts the regenerative process.

One attractive aspect of our model is that it may explain why species and tissues vary in their capacity to regenerate. As we have developed in the second part of this Hypothesis, there has been long-standing co-evolution between TEs and their controllers, which is reflected by the extensive variation in genomic TE content and host defense strategies observed across species. We posit that animal lineages harboring diverse and dynamic TE populations have adapted to control these elements in a great variety of cellular contexts, including tissue regeneration. If true, this model offers the promise of boosting the regenerative capacity of certain human tissues by manipulating TE activity.

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Competing interests

The authors declare no competing or financial interests.

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