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Mobile DNA

REVIEW

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Transposon expression and repression in skeletal muscle

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Abstract

Transposons and their derivatives make up a major proportion of the human genome, but they are not just relics of ancient genomes. They can still be expressed, potentially affecting the transcription of adjacent genes, and can sometimes even contribute to their coding sequence. Active transposons can integrate into new sites in the genome, potentially modifying the expression of nearby loci and leading to genetic disorders. In this review, we highlight work exploring the expression of transposons in skeletal muscles and transcriptional regulation by the KRAB-ZFP/KAP1/SETDB1 complex. We next focus on specific cases of transposon insertion causing phenotypic variation and distinct muscular dystrophies, as well as the implication of transposon expression in immune myopathies. Finally, we discuss the dysregulation of transposons in facioscapulohumeral dystrophy and aging.

Keywords Transposable elements, Skeletal muscle, Muscular dystrophy

Background

Transposable elements (TEs) are DNA sequences that are able or were at one time able to be duplicated and reinserted into the genome. On average, TEs represent 45.6% of mammalian genomes, with high correlation between TE content and genome size [1]. This statistic alone is evidence that TEs have participated in evolution, but are they still contributing to our physiology? While TE regulation has been extensively studied in embryonic stem cells and germ cells, we know much less about their regulation in somatic tissues. Deregulated expansion of TE sequences has frequently been found in cancer genomes, especially epithelial cancers [2, 3]. In normal brain development, TE expression is dynamically regulated [4], and repression of a specific family of TEs is essential for formation of the pancreas [5]. TE regulation may also be an important component of regenerative processes [6]. Skeletal muscle is a highly regenerative tissue and the focus of this review is on how TEs directly and indirectly influence skeletal muscle in various contexts, including regeneration, disease, and aging.

Introduction to TEs

The discovery of transposable elements by Barbara McClintock was a major genetic breakthrough of the last century [7]. TEs are thought to play a major role in the evolution of species and are especially prevalent in eukaryotes [8]. Certain TE sequences contain binding sites for transcription factors, and their spread has had a major impact on gene regulatory networks [9], reviewed in [10]. As an example, the MER41 transposon has been co-opted by the interferon signaling pathway involved in innate immune signaling [11]. Individual copies of the transposon have distributed binding sites for the STAT1 transcription factor near multiple genes of the pathway, allowing for their synchronized upregulation upon interferon stimulation.

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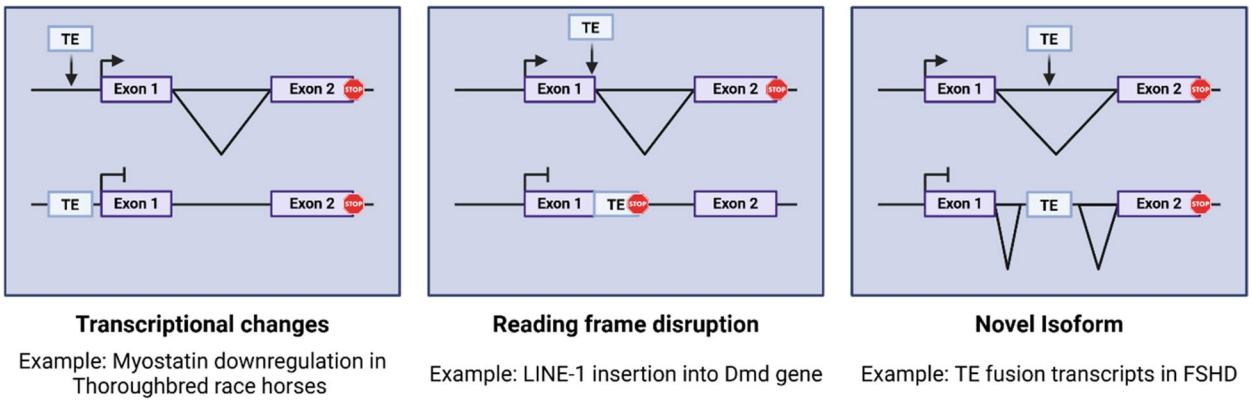

Fig. 1 Transposon insertion effects on coding genes. Examples from muscle studies are given. Left: TE insertions can affect transcription of nearby genes, possibly as carriers of binding sites for transcription factors like KRAB-ZFPs. Middle: The insertion of a TE inside a gene can lead to inclusion of the TE sequence inside a coding transcript, leading to frameshifts, early stop codons or nonsense-mediated decay. Right: TE insertions can generate novel protein isoforms with new functional domains

TEs can be separated into two main classes via their transposition mechanism [12]. Class I TEs, also known as retrotransposons, represent around 44% of the human genome. They depend on a copy-and-paste mechanism of their RNA to transpose [13, 14]. Retrotransposons are mainly long terminal repeat (LTR) retrotransposons represented in humans by the human endogenous retroviruses (HERVs) and their subtypes, or non-LTR retrotransposons [12, 15]. This nomenclature comes from the presence of LTR sequences derived from the original retroviral genome, necessary for viral packaging. Non-LTR retrotransposons consist of three subfamilies: Long Interspersed Nuclear Elements (LINE), Short Interspersed Nuclear Elements (SINE) and SINE-R/VNTR/Alu (SVA) elements [16–18]. Class II TEs are defined as DNA transposons that mobilize using a cut-and-paste strategy [12].

With the advent of progressively more advanced sequencing technologies, it is clear that transposon activity has and continues to affect all tissues, including the skeletal muscle. This review will highlight different instances of transposon insertion consequences, including changes in expression of nearby genes, disruption of open reading frames and modification of splicing patterns (Fig. 1). These modifications can be beneficial or detrimental to muscle health. However, many insertions are neutral, having no impact on muscle fitness, and thus less studied.

Skeletal muscle and regeneration

Healthy skeletal muscle is largely composed of contractile, multinucleated myofibers, with a supporting cast of stem cells, endothelial cells, fibroblasts, and resident immune cells. These distinct cell populations contribute to general tissue function, but can be rapidly mobilized for repair after injury. The regeneration process in skeletal muscle is orchestrated around the activation of the essential satellite cells (also known as muscle stem cells) and their commitment to a synchronized myogenic program [19]. Genetic ablation studies have also shown requirements for macrophages and fibroblasts in efficient regeneration [20, 21]. Muscle satellite cells undergo remarkable epigenetic and transcriptional changes during regeneration [22, 23], and reestablish the satellite cell pool once repair is completed [24]. The three key phases of the process are inflammation, regeneration and remodeling. Briefly, damaged myofibers are resorbed by macrophages in the first days following injury, while satellite cells undergo activation associated with metabolic and epigenetic modifications, and extensive proliferation before differentiating to form new myocytes, which fuse together to form large, multinucleated myofibers. A subset of activated satellite cells will self-renew to restore the pool of quiescent muscle stem cells [25]. Despite few studies on TE expression states during skeletal muscle regeneration, several groups have highlighted the importance and the role of TE balance between activation and repression in the regeneration process in other tissues, especially in regulation of the inflammatory stages, stem cell potency and equilibrium between pro-inflammatory and anti-inflammatory states [6].

Transposon expression in skeletal muscle

The first reports of transposon expression in skeletal muscle came from bioinformatic analysis of expressed sequence tags (ESTs). 0.82% of ESTs expressed in human skeletal muscle contained endogenous retrovirus sequences [26]. This study used Repeatmasker and Repbase version 7.2 [27] for transposon assignment, and

GenBank Flat File (Release 131) and UniGene (Build 154) for EST analysis. Bioinformatic resources for transposon expression analyses have improved significantly in the last two decades, and therefore it is probable that these early estimates should be revisited. Using RT-PCR the same group showed that the *envelope* (*env*) gene of HERV-H is expressed specifically in the skeletal muscle, placenta, spleen and thymus, as well as a number of different cell lines [28]. Other groups also showed through bioinformatic analysis that specific retrotransposons and primate-specific Alu elements are included in gene exons specifically in the muscle [29, 30]. While rare, 4 human genes with transposon inclusion in coding sequence were identified in the first study [29]. In the second study, researchers focused on the inclusion of Alu sequences and found a muscle-specific inclusion in selenoprotein 1 (SEPN1), a gene implicated in a rare muscular dystrophy [30]. The inclusion was more prevalent in human muscle transcripts as compared to macaque and chimpanzee, suggesting recent evolutionary changes. With the development of antibodies recognizing env protein from specific retrotransposons, researchers showed that ERV3 TEs are translated in human muscle [31]. The analysis of RNA-seq data from rat tissues revealed relatively few TEs specifically expressed in the muscle, in comparison with other tissues including the testis and brain [32]. However, Cap Analysis Gene Expression (CAGE) data from mouse tissues showed tissue-specific expression patterns of different retrotransposons, including in the muscle [33].

The studies described above examined transposon expression at the level of the entire muscle, but the muscle is made up of many distinct cell types, including myofibers, satellite stem cells, vascular, immune and mesenchymal cells. It will be important to determine the individual cell types expressing specific transposons with single cell/nuclei RNA sequencing and algorithms such as SoloTE [34].

It remains to be seen whether the expression of many of the above TEs has an impact on muscle physiology, or if they are just expressed due to nearby gene transcription. However, there are specific regulatory pathways required for TE silencing, that are now known to be crucial for skeletal muscle regeneration.

Transposon repression in muscle

The majority of TEs are epigenetically silenced, especially by methylation of DNA and histone 3 lysine 9 (H3K9). While several different systems for this silencing have been identified, one of the most well-characterized is the Krüppel-associated box zinc finger protein (KRAB-ZFP) family of transcription factors, which recruit the repressive cofactor KRAB-associated protein 1, also known as Tripartite motif containing 28 (KAP1/TRIM28), along with the H3K9 methyltransferase Su(var)3–9, Enhancer of Zeste and Trithorax domain bifurcated histone lysine methyltransferase 1 (SETDB1) to TE sequences for methylation and epigenetic repression. [35–37]. (Fig. 1). KRAB-ZFPs compose the largest transcription factor family in humans and include more than 350 different encoded proteins [38]. They are distinguished by their classical structure of a KRAB domain at the N-terminus and a C2H2 zinc finger array at the C-terminus [39]. The zinc fingers bind DNA targets and recruit KAP1/TRIM28 via the KRAB domain [40]. The N-terminal domains of KAP1 directly interact with the KRAB domain, while the C-terminal portion contains a plant homeodomain (PHD) finger and a Bromodomain, which are crucial for recruiting the NuRD histone deacetylase complex and the H3K9-specific methyltransferase SETDB1, aiding in chromatin condensation [41, 42]. These domains promote the formation of heterochromatin marked by low histone acetylation and high tri-methylation of H3K9 (H3K9me3).

KRAB-ZFPs display cell type-specific patterns of expression [9, 43], suggesting they may be regulating cell-specific features. Concordantly, the deletion of their cofactor KAP1 derepresses distinct TEs in different tissues [43]. In the C2C12 mouse myoblast cell line, KAP1 knockdown led to upregulation of MERVK10C-int, while SETDB1 knockdown upregulated MERVK10C, IAP-d and IAPEz TEs, all of which are subclasses of ERVKs.

In the same cell line KAP1 has been found to orchestrate myogenesis through the control of myoblast determination protein 1 (Myod) and myocyte-specific enhancer factor 2d (Mef2d) [44]. In proliferation conditions, it was suggested that KAP1 acts as a scaffold by targeting MYOD and MEF2D, bound to myogenesis regulatory regions, and recruits euchromatic histone-lysine N-methyltransferase 2 (EHMT2, also known as G9a) and histone deacetylase 1 (HDAC1) as chromatin inhibitors and E1A binding protein p300 (EP300) and lysine-specific histone demethylase 1A (LSD1) as chromatin activators. KAP1 maintains a strong silencing effect, until differentiation signals induce a Serine 473 (Ser473) specific phosphorylation by mitogen- and stress-activated protein kinase-1 (MSK1), releasing the G9a and HDAC1 inhibition and allowing the MYOD/MEF2D complex to induce differentiation [44]. Interestingly, phosphorylation of KAP1 at Ser473 is known to be induced by DNA damage [45]. KAP1 may also regulate differentiation of myoblasts through repression of miR-133a [46]. While the authors propose mechanisms for KAP1-mediated regulation of myogenic differentiation, the link with KZFPs and TE regulation was not explored. It is also possible that myogenic transcription factors and a KAP1-KZFP complex bound nearby sites in the DNA, without direct

Table 1 Muscle-specific expression of TEs. The classification of TE comes directly from the nomenclature of the cited reference. Note that all upregulated TEs in mouse myoblasts and satellite cells with knockdown/knockout of KAP1 or SETDB1 belong to the ERVK or ERV1 class

Tissue/cell type	Condition	TEs expressed	Reference
Human muscle	healthy	HERV-H (LTR)	[28]
Human muscle	healthy	ERVK(LTR) Alu, L2 (non-LTR)	[29]
Human muscle	healthy	Alu (non-LTR)	[30]
Human muscle	healthy	ERV3 (LTR)	[31]
Rat muscle	healthy	MER74A, MER73-int, HERVL40 (LTR), Arthur1 (DNA)	[32]
Mouse muscle	Bag3 heterozygote and Bag3 knockout	LINE.RTE (non-LTR)	[33]
C2C12 (mouse myoblast cell line)	KAP1 knockdown	MERVK10C-int (LTR)	[43]
C2C12 (mouse myoblast cell line)	SETDB1 knockdown	MERVK10C, IAP-d, IAPEz (LTR)	[43]
Mouse satellite cells	Setdb1 knockout 60 h post cardiotoxin injury	MMERVK10C-int, RLTR45, MMERVK10D3_1-int, ERVB4_2-1_MM-int, IAPEz_int, RLTR10D2, RLTR45-int, RLTR6-int, RLTR6C_Mm, MuLV-int (LTR)	[53]

interaction. Furthermore, myogenic cell lines lack the complexity found in skeletal muscle in vivo. Fortunately, recent studies have investigated the role of KAP1 in specific cell types of mouse skeletal muscle.

In mice, KAP1 was reported to be involved in the regulation of muscle fiber size. It was reported that maximal intensity contractions experiments (inducing hypertrophy), demonstrated a robust Ser473 phosphorylation of KAP1. KAP1 muscle-specific knock out (KO) mice had an attenuated hypertrophy response, while hypertrophy was induced upon expression of a Ser473 phosphomimetic mutant. In addition, KAP1 absence led to a decrease in muscle mass, smaller glycolytic fibers and altered contractions [47]. A follow-up study showed that KAP1 partially regulates muscle size through a protein degradation-mediated pathway, specifically via Mettl21c, a skeletal muscle-specific protein methyltransferase. The overexpression of Mettl21c causes an increase in muscle size, inducing hypertrophy. However, it is not clear if KAP1 and Mettl21c have a direct or an indirect interaction as protein degradation studies represent a challenge in the muscle field [48]. More work is also required to see whether or not TE repression is involved in this pathway.

When KAP1 is inducibly deleted in the satellite cells of the muscle, there is no impact on their number two weeks following tamoxifen induction [49]. However, KAP1 KO satellite cells are not able to regenerate the muscle following injury, due to defects in fusion of regenerating myotubes and excessive fibrosis. Elegant genetic experiments demonstrated that this defect does not depend on the phosphorylation of Ser473 detailed above. Mechanistically, the fusion defect appears to be linked to regulation of the Myomixer gene, crucial for myoblast fusion [50–52]. Studies on the impact of transposon expression will be necessary to determine whether loss of KAP1, TE mobilization and myogenesis are functionally linked.

Recent work suggests that active repression of ERV loci by Setdb1 is required in satellite cells to allow skeletal muscle regeneration to proceed [53]. The deletion of the Setdb1 gene in satellite cells has no impact on the muscle during homeostasis, but following cardiotoxin injury, Setdb1 KO satellite cells upregulate a number of HERVs and cytokines, activating cGAS signaling (Table 1). This perturbs immune cell dynamics in the regenerating muscle. Furthermore, satellite cells upregulate cell cycle inhibitor genes and a significant fraction of them undergo apoptosis. These defects lead to major muscle regeneration impairment one month later ([53], Fig. 2). In contrast with the results of the satellite cell knock out of Kap1/Trim28, Setdb1 KO cells showed no defects in fusion of muscle cells in vitro. The authors also show that the deletion of Sedb1 in fibroblasts of the muscle has no impact on muscle regeneration.

The demonstration that satellite cells lacking either Kap1 or Setdb1 cannot effectively regenerate skeletal muscle suggests that transposon regulation plays an important role in this process. In fact, recent work has also implicated Setdb1 in regeneration of the skin [54], suggesting that TE repression may be an important step in regenerative processes in general. However, the individual KRAB-ZFP proteins that recruit KAP1 and SETDB1 to TEs for repression in the muscle are not well defined.

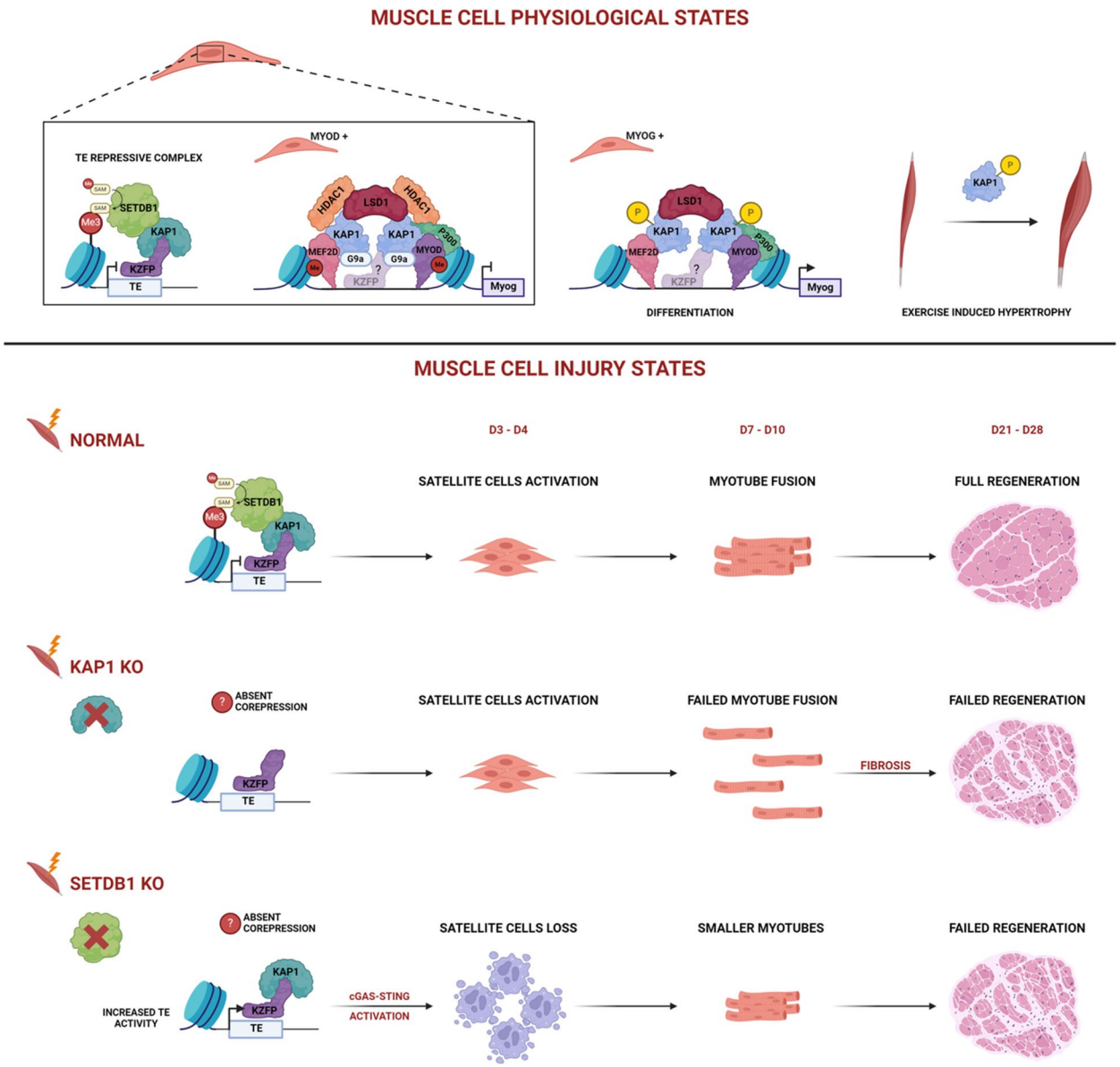

Fig. 2 Roles of KAP1/TRIM28 and SETDB1 in muscle physiology and regeneration. Top: In myogenic cells KAP1 associates with KRAB-ZFPs and SETDB1 to silence TEs through H3K9me3, but also forms a distinct repressive complex at the Myog promoter, a gene essential for differentiation. Phosphorylation of KAP1 leads to dissociation of specific corepressors, allowing Myogenin transcription and differentiation. However, it is possible that a KAP1-KZFP complex and myogenic transcription factors bind to nearby sequences in the promoter, without directly interacting. Phosphorylation of KAP1 is also associated with exercise-induced hypertrophy. Bottom: Consequences of KAP1 or SETDB1 loss in muscle stem cells on muscle regeneration. Normally, satellite cells activate 3–4 days after injury, myotubes fuse between 7 and 10 days post-injury, and regeneration is complete between 21 and 28 days post-injury. When KAP1 is absent from the satellite cells, myotubes do not fuse and excessive fibrosis persists during regeneration. When Setdb1 is knocked out in satellite cells, the CGAS-STING pathway is activated, leading to elimination of satellite cells by the immune system. The early loss of the critical satellite cells abrogates muscle regeneration

Transposons and phenotypic variation in muscle

One consequence of transposon insertion inside or near a gene is a change in its expression. Depending on the gene, this can be beneficial. Insertion of an equine repetitive element 1 (ERE-1) SINE into the Myostatin gene promoter was highly associated with optimum racing distance for Thoroughbred racehorses [55]. Analysis of myostatin levels in the serum of these horses showed a significant drop in heterozygotes relative to wildtypes and even less myostatin in homozygotes for the insertion [56]. Testing the variants with and without the insertion in reporter assays revealed that the promoter

Table 2 TE insertions causing muscle disease

Disease	Genus species	TE	Gene affected	Reference(s)
Duchenne/Becker muscular dystrophy	Homo sapiens	L1 (non-LTR)	Dmd	[65–68]
Fukuyama-type congenital muscular dystrophy	Homo sapiens	SINE (non-LTR)	Fukutin	[71]
Muscular dystrophy	Canis familiaris	L1 (non-LTR)	Dmd	[69])
Muscular dystrophy	Mus musculus	IAP (LTR) and L1 (non-LTR)	Laminin alpha 2	[70]
Centronuclear myopathy	Mus musculus	SINE (non-LTR)	Ptpla/Hacd1	[72])

with the insertion caused a 4- to sevenfold reduction in expression, depending on the species of cells transfected (horse or human) [57]. Thoroughbred horses with the insertion had a decrease in type 1 oxidative myofibers and an increase in type 2B glycolytic myofibers in the middle gluteal muscle [58]. Non-transposon mutations in myostatin have been associated with increased muscle mass in multiple species, including cows and mice [59, 60]. The extensor digitorum longus (EDL) muscle of Myostatin knock-out mice also displays an increase in type 2B glycolytic myofibers, and wildtype mouse EDL muscle expresses low levels of myostatin [61].

The syncytin genes are derived from the env gene of an endogenous retrovirus, and are essential for placentation in mice [62, 63]. They encode fusogenic proteins, allowing for the formation of cellular syncytia, in which one cytoplasm contains multiple nuclei. The placenta and mature myofibers are both examples of syncytia. The deletion of syncytin-B compromises muscle development and regeneration, but exclusively in male mice [64]. In vitro, knock down of syncytin genes reduced fusion in primary myoblasts from human, sheep and dog. This suggests that these retrovirally derived genes have had a major impact on mammalian musculature, as well as formation of the placenta.

Transposons and muscular dystrophy

Transposons can also insert inside protein-coding genes important for skeletal muscle formation, which can directly affect muscle development or lead to muscular dystrophy (Table 2). One of the first cases identified of a retrotransposon inducing a human disease was described in 1993, in two brothers with Duchenne muscular dystrophy, where a long interspersed nuclear element 1 (LINE-1/L1) copy inserted into exon 44 of the Duchenne muscular dystrophy (Dmd) gene [65]. The insertion induced skipping of exon 44, and thus a frame shift leading to an early stop codon. The study of a family containing 10 individuals with symptoms ranging from the mild Becker muscular dystrophy to Duchenne muscular dystrophy revealed a distinct LINE-1 insertion in exon 48 of the Dmd gene [66]. In this case, exon 48 was skipped, leading to a short, in-frame deletion, consistent with a milder dystrophic phenotype. Additional, distinct LINE-mediated insertions into the Dmd gene have been described [67, 68]. LINE-1 insertion into the Dmd gene is also the origin of a spontaneous dog model of the disease [69]. Sequencing of cDNA from affected Pembroke Welsh corgi dogs revealed 168 bp of LINE-1 sequence containing a stop codon between exons 13 and 14. Another spontaneous model of muscular dystrophy in mice derived from the insertion of retrotransposon sequences into laminin alpha 2, a gene involved in formation of the extracellular matrix and muscle function [70]. The insertion consisted of the 5' LTR of an IAP element (a mouse-specific retrotransposon) and an F-type LINE-1 sequence. Due to compatible splice sites flanking the IAP LTR, it inserted into the mRNA, leading to a stop codon 12 codons later. This eliminated important portions of the protein, causing muscle disease.

The insertion of a SINE and associated repetitive sequences in the Fukutin gene is prevalent in the Japanese population and found in the majority of Fukuyama-type congenital muscular dystrophy (FCMD) patients [71]. This insertion is found in the 3' untranslated region of the gene, and affects the stability of the mRNA, as it is undetectable in patients homozygous for the insertion. In a specific cohort of labrador retrievers, a SINE insertion into exon 2 of the protein tyrosine phosphatase-like A (Ptpla, now known as 3-hydroxyacyl-CoA dehydratase 1 or Hacd1) gene caused centronuclear myopathy [72]. The insertion led to the production of many mRNA variants, and a drop in total transcripts to 35% of wildtype.

Several muscular dystrophies appear to be caused by transposition inside or near genes important for muscle development and function, but the simple transcription of transposons may also contribute to specific myopathies.

Transposon expression in myositis

Idiopathic Immune Myopathies (IIM), also referred to as Autoimmune Myositis (AIM) are a group of acquired autoimmune myopathies characterized by muscle inflammation and a range of muscular and extra-muscular manifestations. Although they were originally classified as Dermatomyositis (DM) and Polymyositis [73], the

current classification includes DM, Immune Mediated Necrotizing Myopathy (IMNM) or Necrotizing Autoimmune Myopathy (NAM), Antisynthetase Syndrome (ASS) and Inclusion Body Myositis (IBM) [74–77]. The Interferon (IFN) system plays a major role in the pathophysiology of these diseases, where IFN type I (IFN-I) is associated mainly with DM and IFN type II (IFN-II) is more predominant in ASS and IBM (reviewed extensively in [78]. An alternative isoform of the interferon receptor alpha and beta receptor subunit 2 (IFNAR2) is produced by exonization of an Alu element, and can modulate type 1 signaling [79]. This isoform was expressed in all human tissues examined, including skeletal muscle.

It has been found that many autoimmune diseases are associated with an upregulation of LINE-1 elements, such as in Sjogren syndrome and systemic lupus erythematous [80]. Recently, studies have shown that LINE-1 expression is positively associated with IFN-1B levels in DM patients [81]. A follow-up study has shown that in DM patients *LINE-1, HERVK14C* and *SVA* elements were all upregulated and that DNMT3A expression was reduced resulting in LINE-1 promoter hypomethylation [82]. The interplay between LINE-1 regulation and the IFN-1 pathway is also known to be regulated by the HUSH complex, where LINE-1 upregulation can activate IFN-1 signaling [83].

Myositis can also present as a medication side effect, such as statin-induced myositis. Statins are drugs used as a preventative medication in cardiovascular patients to reduce endogenous cholesterol synthesis. It has been found that in human myoblasts treated with simvastatin, rosuvastatin or DMSO, high number of TEs were differentially expressed in the simvastatin group, and are associated to statin myopathy pathways such as AKT3 [84].

Facioscapulohumeral dystrophy (FSHD)

In humans, one muscle disease involves upregulation of a specific gene inducing expression of transposons: facioscapulohumeral muscular dystrophy (FSHD). This disease affects specific muscles of the face, shoulders and upper arms, leading to muscle weakness and atrophy [85]. FSHD was linked to a repetitive element, called D4Z4, in chromosome 4, with coding potential for a homeobox transcription factor [86]. D4Z4 repeats were present on other chromosomes, and in other species, including chick, pig and multiple primates. The coding region was later named DUX4 [87], and sequence analysis suggested it was derived by the retrotransposition of the gene DUXC [88]. DUX4 is expressed very briefly, at the 4-cell stage of human embryonic development, during which it binds to the promoters and activates many of the first genes to be expressed in the embryo [89, 90]. Specific TEs, including HERVL, are also activated. The mouse homologue of DUX4, DUX, is expressed at the 2-cell stage of mouse embryonic development, which corresponds to the same transcriptional stage, known as zygotic genome activation. The loss of DUX expression before this stage compromises mouse embryonic development. In human and mouse ES cells, DUX4 and DUX expression are extinguished, respectively, after the next cell division, and are not normally reactivated. However, the most common form of FSHD occurs when the array of D4Z4 repeats on chromosome 4 is reduced to 10 or less [91]. When this situation is paired with a specific polyA signal, the last D4Z4 repeat is functionally capable of producing the DUX4 protein in muscle cells [92]. While expression of DUX4 is nearly undetectable in the muscle of control and FSHD patients, it can be found in ~ 1/1000 FSHD myonuclei [93]. Interestingly, DUX4 overexpression in human myoblasts induces many genes normally expressed at the 4-cell stage, suggesting that the reappearance of an embryonic transcriptional program directly contributes to the pathology [89].

Table 3 TE expression associated with human disease

Disease	TE	Reference
Dermatomyositis	HERVK14C (LTR), L1, SVA (non-LTR)	[81, 82]
Statin-induced myositis	MaLR(LTR), MIR1_Amn, AluSx1, HAL1 (non-LTR)	[84]
FSHD	MaLR (LTR)	[94]

Lentiviral overexpression of DUX4 in human myoblasts modified the expression of more than 1800 genes relative to a GFP control lentivirus [94]. Furthermore, ChIP-seq analysis of transduced cells revealed DUX4 enrichment at Mammalian apparent LTR retrotransposon (MaLR) family elements, also upregulated in human embryos at the 4-cell stage [90] (Table3). RT-PCR experiments confirmed upregulation of MaLR transcripts in transduced myoblasts. The authors suggested that reactivation of retrotransposons might contribute to DUX4 expression-induced apoptosis [95], thus contributing to the FSHD dystrophic phenotype. Reanalysis of the ChIP-seq dataset with a more recent human genome assembly showed that about two thirds of DUX4 binding sites were found in repetitive elements [96]. DUX4 was able to activate transcription from a small proportion of TEs, including some which could function as alternative promoters for human genes. One of these genes, Hey1, represses myogenesis and is highly upregulated in FSHD muscle, suggesting a potential mechanism for transposon upregulation to contribute to the pathology, by blocking the formation of new myofibers. Nanopore long-read sequencing of RNA from rhabdomyosarcoma cells transfected with DUX4 revealed 247 gene endogenous retrovirus (ERV) fusion

transcripts, suggesting additional mechanisms of disease [97].

FSHD is tightly linked to the derepression of DUX4, which in turn appears to activate TE expression. Whether or not these TEs, or the transcripts they induce, contribute to the pathology is an active area of research.

TEs in muscle aging and exercise

Upregulation of LINE elements has been reported in aging mouse and rat muscle [98, 99]. While this was not associated with physiological changes, the authors hypothesized the expression could lead to genomic destabilization and subsequent cellular dysfunction [98]. During muscle aging in mice, Min and colleagues showed that globally, retroelement DNA became more methylated. However, there was also a "regression toward the mean" in which individual elements that were hypomethylated had increases in methylation, while hypermethylated elements lost methylation with aging [100]. These changes were not seen in T cells, a control cell population examined in the study. The expression of retroelements decreased from 2 to 20 months but increased from 20 to 28 months.

LINE-1 DNA content was reduced in the muscle of young mice following treatment with nucleotide reverse transcriptase inhibitors (NRTIs), suggesting that there is active transcription and reinsertion of these sequences in the muscle [101]. In humans, LINE-1 elements become demethylated and their expression increases with aging [102]. However specific exercises in humans and rats can reduce this age-related de-repression [102–105]. In young patients, exercise reduced LINE-1 mRNA content, the translation of the associated open reading frame 2 protein (ORF2p) segment and more importantly increased the number of satellite cells [103]. While the significance of these changes has not been extensively studied, the authors hypothesized that since the AKT pathway is an important regulator of hypertrophy and satellite cell proliferation [103, 106, 107] and L1 inhibition enhances AKT signaling [108], both factors can be linked to the documented changes related to exercise. Recent work has shown that expression of HERV-W transposons increased in the blood of patients following strength training [109], but it is unclear if the muscle is the source of expression. More research is needed in the field of muscle aging, but transposon expression appears to hold some promise as a biomarker and potential target of rejuvenating muscle treatment.

Conclusions

TEs have undoubtedly played a major role in genome evolution, but their current participation in muscle physiology requires additional studies. There is clear mouse genetic data to suggest that TEs should be switched off in muscle stem cells for muscle regeneration to occur, but there are many more pieces of the puzzle to be investigated. It will be of particular interest to see if this regulation is important in other muscle cell types. Depending on the genomic context, the insertion of a transposon can improve running performance, or lead to severe muscular dystrophy. In some cases, even the transcription of transposons may be sufficient to cause muscle disorders. Retrotransposition is a common mode of gene duplication, but in the case of DUX4, expression of the gene can also lead to muscle disease, potentially through upregulation of additional TEs. Recent work suggests that transposons can be reactivated during muscle aging, though the consequences of this reactivation require further study. Thanks to rapid advances in sequencing technologies and sensitivity, answers to open questions about transposons in muscle biology are just around the corner, as are-inevitably-more questions.

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Authors' contributions
MB, LZ and FR all contributed to the writing of the manuscript, and have all read and approved the final manuscript.

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Data availability
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Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
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Competing interests
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