reverse process) might shed light on how protein aggregation can be reversed, given that synthetic polymers can easily be engineered to mimic the properties of proteins.

Another intriguing attribute of Fu and colleagues' tactoids is that they can self-assemble into larger-scale structures. For example, the authors observed that tactoids on a glass coverslip aligned perpendicularly to the surface, forming an array. At first, the tactoids could diffuse laterally on the surface and coalesce. But as they aged and grew longer, they stopped coalescing and tilted, creating a forest of leaning spindles. This indicates that supramolecular polymers can undergo hierarchical assembly processes, from the nanoscale (supramolecular polymer subunits) to the millimetre scale (assemblies of tactoids), which could potentially be used to fabricate microscale bristles that, in turn, serve as scaffolds for larger structures.

By contrast, tactoids on a liquid surface formed distorted, crown-like shapes. Fu *et al.* observed this by dissolving UPy–Gly molecules in a system in which droplets of one polymer (dextran) form in another immiscible liquid polymer (polyethylene glycol; PEG). The supramolecular polymer formed from UPy–Gly at first dissolved into the PEG, but then formed condensates at the surface of the dextran droplets, eventually encapsulating the droplets. The authors found that continuous or discrete supramolecular networks could be formed at the surface of the droplets by varying the pH and concentrations of salts in the system. Similar condensation behaviour to that of UPy–Gly was observed when other supramolecular polymers were tested in the PEG–dextran system, indicating that LLPS is a general phenomenon for supramolecular polymers.

Fu and colleagues' study shows that supramolecular polymers are not immune to the laws of physics that prevail in other systems at different scales. For example, the entropic driving force that causes the condensation of the tactoids is also responsible for the condensation of liquid-crystal mesogens — nanometre-scale molecules that form liquid crystals. The authors' findings therefore open up the possibility of using supramolecular polymers as models of liquid-crystal behaviour. Although biological fibres and rods, such as virus particles, microtubules and actin filaments, have also been shown to act like liquid-crystal mesogens at the micrometre scale[13–18], they are difficult to modify. By contrast, there are many ways to modify the aspect ratio, chemical nature and chirality (handedness) of tactoids formed from synthetic supramolecular polymers, enabling them to be used as micrometre-scale models that closely relate to the molecular-scale liquid-crystal mesogens that are of interest to researchers. Future studies of the self-assembly of liquid crystals formed from supramolecular polymers might reveal the hierarchical organization of the world, from the nano- to the macroscale.

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Evolution

Mobile DNA explains why humans don't have tails

Miriam K. Konkel & Emily L. Casanova

The lack of a tail is one thing that separates apes — including humans — from other primates. Insertion of a short DNA sequence into a gene that controls tail development could explain tail loss in the common ancestor of apes. **See p.1042**

Tails are a common feature in the animal kingdom, and all mammals have a tail at some point during embryonic development[1]. In humans, the tail disappears at the end of the embryonic phase — approximately eight weeks *in utero*[2] — although internal parts remain in the form of the tailbone. The loss of the tail is considered a distinctive characteristic of apes and might have influenced our own upright walking style. On page 1042, Xia *et al.*[3] report that the insertion of a type of mobile genetic sequence that moved around the genome during evolution, known as a transposable element, could be associated with the loss of the tail.

Most monkeys have a tail, and tails were present at the origin of the primate lineage more than 65 million years ago[4]. In fact, the absence of a tail is one way to distinguish apes from monkeys. This characteristic, or phenotype, is shared across all apes, suggesting that tail loss coincided with, or occurred shortly after, the rise of apes after they diverged from their last common ancestor with monkeys around 25 million years ago.

With this knowledge, Xia and colleagues compared prime candidate genes for tail loss across the genomes of several primate species, initially focusing on exons (the regions of DNA that code for proteins). When this approach turned out not to be fruitful, the authors extended their investigation to non-protein-coding regions that were upstream or downstream of the genes, or in the genes themselves. The latter regions are known as introns, and they commonly interrupt protein-coding sequences. Xia and colleagues found that a type of primate-specific transposable element called an Alu element[5] was inserted in an intron of the *TBXT* gene — but only in apes, and not in other primate lineages. *TBXT* is also known as *Brachyury* (meaning 'short tail') because mutations in the gene have been associated with short tails in several species, including Algerian mice (*Mus spretus*)[6] and Manx cats (*Felis catus*)[7].

But how can the insertion of a short, roughly 300-base-pair Alu element into the non-coding sequence of a gene contribute to a tailless phenotype? To answer this, Xia and colleagues further scrutinized the entire *TBXT* gene and identified another Alu element oriented in the opposite direction (inverted) in intron 5. Because inverted Alu sequences in close proximity can pair up and create double-stranded RNA structures, the authors proposed that exon 6, which resides between the two Alu sequences, might be removed from the RNA transcript straight after transcription in a process called splicing (Fig. 1).

To determine whether these two Alu sequences create alternatively spliced versions of *TBXT* RNA transcripts, Xia and colleagues took human and mouse embryonic stem cells and differentiated them so that

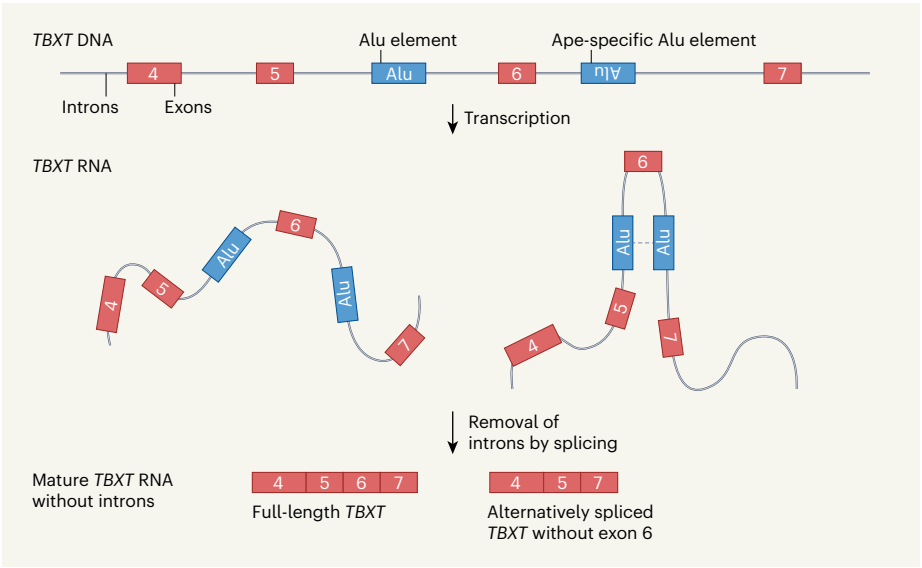

Figure 1 | An ape-specific alternative RNA transcript of a tail-development gene. The *TBXT* gene is involved in tail development. Xia *et al.*[3] compared *TBXT* sequences across primates, and identified a short mobile DNA sequence, known as an Alu element, that is inserted into a non-protein-coding region (intron) of *TBXT* in apes but not in other primates. When DNA is transcribed into RNA, the interaction of this Alu element with another nearby Alu element, which is not specific to apes and is oriented in the opposite direction, can lead to the removal of a protein-coding region (exon) during splicing, resulting in two possible versions of mature RNA — one that is full-length and one in which exon 6 is missing. Expression of this exon-skipped *TBXT* might have contributed to tail loss as early apes evolved.

they mimicked the developmental state in which *TBXT* is expressed and implicated in tail development. Mouse cells, the genomes of which do not contain the primate-specific Alu insertions, expressed only the full-length *Tbxt* transcripts, but human cells expressed both the full-length transcript and a shorter transcript that did not include exon 6. Removing either Alu element using the gene-editing tool CRISPR–Cas9 resulted in an almost-complete loss of the transcript that lacked exon 6.

To tie the altered transcripts to the tailless phenotype observed in apes, Xia *et al.* created several mouse lines. One mouse model simply had exon 6 of *Tbxt* deleted. To confirm that highly similar sequences oriented in opposing directions (reverse complementary sequences) could result in alternative splicing and therefore the skipping of exon 6, they also created 'humanized' mouse models by modifying the intron sequences flanking exon 6 of *Tbxt*. They did so by integrating either a pair of reverse complementary Alu sequences or a pair of reverse complementary mouse-specific sequences.

The authors confirmed that mice lacking the functional, full-length *Tbxt* RNA transcripts did not survive to birth[6,7], and found that mice with one intact copy of the gene and one altered copy had variable phenotypes, ranging from being tailless to having a full-length tail. However, the humanized mouse model with reverse complementary Alu sequences flanking exon 6 did not have a tailless or shortened-tail phenotype. This raises the question of whether tail loss is indeed solely driven by the ape-specific Alu insertion, or whether other contributing factors are required. Intriguingly, inserting mouse-specific reverse complementary sequences did result in a shortened-tail phenotype in mice. Xia *et al.* made another exciting finding: all mice with one copy of *Tbxt* in which exon 6 was deleted and one copy with the insertion of the reverse complementary mouse-specific sequences lacked a tail.

Together, the data support the role of the ape-specific Alu insertion in contributing to the tailless phenotype in apes. Furthermore, the authors observed that mice that expressed high levels of the exon-skipped gene transcript had an increased risk of defects in the embryonic structure that later forms the brain and spinal cord, known as the neural tube. Thus, the authors raise the possibility that tail loss in our ape ancestors might have come with the price of having an increased risk of neural tube defects.

So, why did early apes lose their tails? Some researchers interpret the loss as adaptive, meaning it would have provided an evolutionary advantage. This is an idea that Xia *et al.* also engage with, echoing previous ideas that the loss of the tail contributed to improved two-legged (bipedal) locomotion. Research in human transitional species, such as *Ardipithecus ramidus*, suggests that bipedalism initially evolved in our tree-dwelling ancestors and was later used for a ground-dwelling lifestyle[8]. Scientists have tended to focus on adaptive explanations of tail loss and how it might enable human mobility, but several lines of evidence suggest that having a tail does not hinder bipedalism, and could in fact support it. For example, tails seem to help to maintain posture in capuchin monkeys (*Sapajus libidinosus*) when they are transporting stone tools and walking bipedally[9]. Although humans regularly transport loads bipedally, robotics research suggests that a waist-mounted 'tail' can increase stability[10], meaning that a tail could be adaptive even for modern humans.

Physical isolation of primate populations offers an alternative explanation. Tectonic activity that began around 25 million years ago in East Africa, accompanied by volcanism, lake development and the reorganization of river networks, led to notable shifts in climate and the availability of resources. These geographical changes might have happened at the same time as the early apes started to evolve[11]. Early ape ancestors could have become isolated because of climate upheaval. With small population sizes, random genetic drift — such as the fixation of the Alu insertion reported by Xia *et al.* — could have played a larger part than did selection in tail loss[12]. Thus, altered function of the *TBXT* gene in early apes could have resulted from genetic drift in a small, reproductively isolated population, as an adaptive response, or both.

Although the ultimate causality might remain unknowable, Xia and colleagues' results offer a deeply compelling new chapter in the tale of our tail, and identify ways by which transposable elements can contribute to the diversification of the human repertoire of gene expression and, ultimately, typical human features.

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