nacre comes from an in vivo experiment, in which Suzuki *et al*. injected double-stranded Pif messenger RNA (mRNA) into oyster tissue. This treatment was expected to activate the cellular RNA interference machinery, which catalytically degrades all endogenous mRNA molecules whose sequence matches the introduced double-stranded RNA. Indeed, in injected specimens, the Pif mRNA level was decreased by ~50%, suggesting that the amount of Pif-protein complex has also been substantially reduced. The injected specimens showed dramatically reduced biomineralization and completely lost the ability to form the lamellar sheets of nacre. Instead, they formed rather disordered biomineral structures. Altogether, the in vivo and in vitro results strongly suggest that Pif80 and Pif97 are directly involved in creating the layered arrangement of aragonite platelets in nacre.

Previously, the protein Starmaker has been shown to be essential for the formation of the layered aragonite structure of otolith biominerals in zebrafish (*6*). Both this protein and Pif80 and Pif97 are rich in the amino acid aspartate. Indeed, aspartate-rich proteins appear to be a common tool of biomineral-forming organisms, irrespective of the chemistry of the mineral phase. They are involved in the formation of calcium phosphate biominerals of bone and teeth (*7*) and the amorphous silica cell walls of diatoms (*8*).

Nature's ability to generate with ease amazingly complex and functional inorganic structures is the envy of materials engineers. Knowledge of the molecular details of biomineralization processes is key to enable biomimetic syntheses of new high-performance composite materials (*9*, *10*). Suzuki *et al*. show that it is important to characterize the previously neglected protein components of the organic framework. Several as yet uncharacterized proteins are present in the extracts prepared by Suzuki *et al*., and even more may be found using different procedures for protein extraction. Furthermore, the effectiveness of the Pif mRNA "knockdown" experiment will strongly encourage the community to use analogous approaches to investigate the in vivo function of other mollusk shell proteins.

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GENETICS

MITEs—The Ultimate Parasites

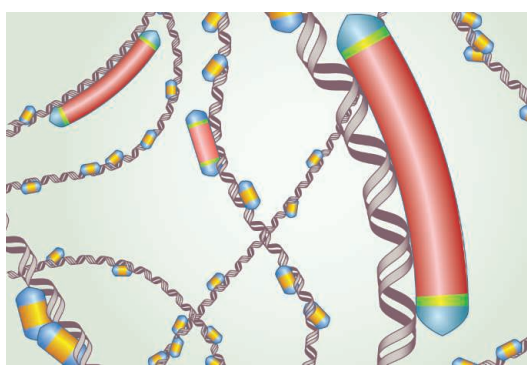
How do genomic parasites called MITEs accumulate in large numbers in plant genomes?

Josefa González and Dmitri Petrov

Transposable elements (TEs) are fragments of DNA that can jump from one genome position to another, often producing extra copies of themselves in the process. Sequences generated by TEs are the most abundant component of practically all eukaryotic genomes. For instance, about 90% of human DNA is made up of TEs. They are potent sources of mutation: In *Drosophila*, TEs are responsible for 50 to 80% of the visible spontaneous mutations (those that result in a visible phenotypic change) (*1*) and can generate a wide spectrum of mutations, from subtle regulatory changes to gross genomic rearrangements. On page1391 of this issue, Yang *et al*. (*2*) show how a special type of TEs, called miniature inverted repeat transposable elements or MITEs, transpose and accumulate in the genome.

A canonical TE contains several genes that promote its mobility around the genome. There are two main types of TEs. Class I TEs encode a reverse transcriptase and move around by reverse transcription of their own mRNA. Class II TEs encode transposases that cut the TE sequence from the genome and insert it into a different location. Both classes parasitize the key cellular functions of transcription, replication, translation, and repair to promote their spread in the genome. In most cases they do not seem to provide much benefit to the organism. At times they acquire important cellular functions (such as providing telomeres in *Drosophila*) (*3*), but their persistence in the genome in most cases is likely a result of parasite/host coevolution.

Augustus De Morgan famously declaimed, "Great fleas have little fleas upon their backs to bite 'em, and little fleas have lesser fleas, and so ad infinitum" (*4*). If TEs are parasites of key cellular functions, it is not surprising to find that TEs have their own parasites. These parasites of parasites—less judgmentally called nonautonomous TEs—contain a recognition sequence required for mobility but do not make the protein products (such as reverse transcriptase or transposases) required for transposition. Instead, they rely on full-length, autonomous TEs to provide all protein components. For example, *Alus* (class I TEs that are parasites of long interspersed nuclear elements or LINEs) have been spectacularly successful at spreading around the human genome—much more successful than the full-length long LINEs themselves.



Distant relations. Most TEs are likely to be intragenomic parasites. Autonomous TEs (red) have their own parasites. Some of these are closely related to full-length TEs but have internal deletions and have thus lost their transposase activity (smaller red rectangles). In contrast, MITEs (yellow) are more distantly related, sharing only their TIRs (blue arrows) with the full-length TEs. The rice genome contains thousands of copies of MITEs.

Another extremely successful type of TE was first discovered in plants (*5*). These TEs, called MITEs, are nonautonomous elements that are small (~100 to 500 base pairs) and contain terminal inverted repeats

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(TIRs). MITEs were recognized as key components of plant genomes only after substantial amounts of sequence data from plant genomes—especially rice—became available. They were soon also found in several animal genomes, including mosquitoes, fish, and humans (*6*). However, plants, and in particular rice, continued to be the model organisms to study MITEs, because these and other TEs are still actively reshaping their genomes.

In plants, most MITEs can be classified into one of two superfamilies: *Tourist*-like or *Stowaway*-like. Some MITE families, such as the *Tourist*-like *mPing* family, show sequence homology with full-length TEs in the genome, indicating that they have originated through internal deletions of those full-length elements. These copies retain their TIRs and can thus still bind and be mobilized by the transposases encoded by the full-length elements (*7*).

However, most known MITEs, such as the *Stowaway* family in rice, do not show sequence homology with any other TE in the rice genome. What is the origin of these MITE families? And, given that they are not related to any autonomous copy in the genome, which transposase(s) do they use to jump in the genome? These particular MITE families are present at the highest copy numbers in the genomes; for instance, there are more than 22,000 *Stowaway* MITEs in the rice genome. Thus, this unknown mechanism must be extremely efficient.

Genome-wide analysis of the sequence of two rice subspecies suggested that MLEs (mariner-like elements, a type of TEs) were the most likely sources of transposase activity for *Stowaway* MITEs, although the sequence similarity between the MITEs and the MLEs is restricted to their TIRs (*8*). Based on these genome analyses, Feschotte *et al*. proposed that the thousands of *Stowaway* MITEs in the rice genome were mobilized by the transposase encoded by a small number of distantly related MLEs.

Yang *et al*. have now experimentally validated this model. To do so, they have adapted an assay previously developed in yeast to demonstrate the transposition of a nonautonomous version of a full-length element by its own transposase (*7*). Using this assay, Yang *et al*. studied seven MLE transposases, representing all MLE subclades in rice. They show that six of these transposases can mobilize 17 different *Stowaway* elements, spanning the diversity of *Stowaway* families in this species. Furthermore, using site-directed mutagenesis, they show that the 3′ subterminal region (adjacent to the TIR) of Osm14NAS (one of the rice MLEs used in the assay) represses its own mobilization; in contrast, *Stowaway* MITEs not only lack this repressive motif but also have several other motifs throughout their internal region that promote mobilization.

These results contribute to the understanding of how TEs co-evolved with their host. They not only explain how *Stowaway* MITEs transpose and amplify but also provide clues to why these MITEs reach such high copy numbers, whereas MITEs that are deletion-derivatives of full-length TEs are present in much fewer copies. The deletion-derivate elements most likely retained the subterminal region that represses their mobilization. Full-length TEs evolved to reduce their own mobility, possibly helping them to stabilize their copy number and therefore to persist in the genome (*9*).

Although the mystery of MITE transposition appears to have been resolved with this work, it generates many more questions. For instance, did *Stowaway* MITEs lose their repressive motifs or did they evolve from elements that lacked them? And why do full-length MLE TEs contain repressing sequences? Under what circumstances do MITEs amplify? What limits their spread in the genome? How frequently do MITE insertions alter gene expression or gene products?

TEs are probably as old as life itself and have been an integral, active, and both destructive and constructive component of genomes. A full comprehension of genome evolution and function requires a thorough understanding of the functional roles, evolution, and population dynamics of TEs. The findings of Yang *et al*. contribute to our knowledge of this extremely active and major component of the genome and will fuel studies aimed at the elucidation of intricate interactions among different TEs and between TEs and their hosts.

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NEUROSCIENCE

Went Fishing, Caught a Snake

Dies Meijer

A sinuous receptor links cAMP signaling to myelin formation by Schwann cells in the vertebrate nervous system.

A highly ordered, insulating layer of lipids and proteins known as the myelin sheath surrounds neuronal axons in our nervous system, allowing the rapid conduction of electrical impulses along nerve fibers. Myelin is laid down and maintained by dedicated neuroglia cells—oligodendrocytes in the central nervous system and Schwann cells in the peripheral nervous system. Formation of the myelin sheath is under strict axonal control and involves the wrapping of vast amounts of glial membrane around axons (*1*). The process is initiated by axon-glial cell contact, which elicits an adenosine 3′,5′-monophosphate (cAMP) signal within the glial cell. This signal drives myelin formation (*2*), but the molecular nature of the communication that triggers it has not been clear. On page 1402 of this issue, Monk *et al*. (*3*) provide compelling evidence for a cell surface receptor in Schwann cells that induces cAMP and myelin production in response to the targeted axon.

An increase in the intracellular concentration of cAMP can partially restore the expression of myelin proteins in cultured mammalian Schwann cells, suggesting that cAMP is part of the signaling pathway that drives myelin formation in vivo. Inhibition of protein kinase A, the major target of cAMP, blocks myelination in cultured cells (*4*). Monk *et al*. report that gpr126, a heterotrimeric guanine nucleotide–binding protein (G protein)–coupled receptor, controls this signaling pathway.

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