

Meeting report

Mobile DNA: genomes under the influence

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Mobile DNA is a relatively loose term that encompasses an amazing diversity of genetic elements that are capable of movement from one genomic locale to another, and can often invade other genomes. Transposable elements (transposons), among the most widespread forms of mobile DNA, populate the genomes of most living organisms and have propagated to enormous numbers in many eukaryotes (for example, about half of the human genome is directly derived from transposable elements). An understanding of the behavior of transposable elements is therefore essential to our understanding of how genomes function and evolve. A recent conference on mobile DNA provided many outstanding examples of research in this rich and vibrant field, a few of which are highlighted here. We focus on work that advances our understanding of the impact of transposable elements on the evolutionary trajectories of their host genomes.

The influence of transposable elements on genome structure

With the advent of genomics, the significant influence of transposable elements in shaping the genomes of virtually all organisms is becoming fully appreciated. Most of the transposable elements in mammalian genomes are retrotransposons, transposable elements that transpose via an RNA intermediate. More than a million copies of the *Alu* retrotransposon occur scattered throughout the human genome. Mark Batzer (Louisiana State University, Baton Rouge, USA) reported work showing that nearly 500 events of non-reciprocal recombination between these interspersed *Alu* elements have removed around 400 kb of human genomic DNA since the divergence of the human and chim-

panzee lineages. Prescott Deininger (Tulane University, New Orleans, USA) speculated that the trigger for these recombination events could be the enzymatic machinery encoded by a few active long interspersed nuclear elements (LINE-1 elements) remaining in the genome. Indeed, Deininger reported the stunning observation that the endonuclease activity encoded by a single active LINE-1 can create hundreds of DNA double-strand breaks per cell, the vast majority of which do not result in transposition events but could elicit recombination between adjacent repeats. Genomic havoc wreaked by transposable elements is not limited to primate genomes. Julian Parkhill (The Sanger Institute, Cambridge, UK) reported that intrachromosomal recombination mediated by transposable elements is also responsible for genome shrinkage in some species of the bacterial genus *Bordetella*.

The seemingly chaotic propagation of transposable elements within genomes provides an abundant source of chromosomal rearrangements and new gene arrangements for selection to act on. Alfredo Ruiz (University of Barcelona, Spain) showed that *Foldback*-like transposons mediate recurrent inversions in the chromosome arms of *Drosophila buzzatii*, some of which appear to be selectively maintained in natural populations and thus to be advantageous. Batzer described how movement of some members of the recently discovered SVA family of elements, a relatively new player on the primate retrotransposon scene, had promoted the duplication and dispersal of the *AMAC* gene family in the lineage of African great apes. This occurred by a process known as 3'-transduction, in which a sequence downstream of the SVA element is moved to the new chromosomal site together with the transposon.

Another way in which retrotransposons can augment the gene repertoire of their hosts is through the illegitimate action of the reverse transcriptase they encode on the cell's mRNAs. This generates new DNA copies of cellular genes

that become inserted, or retroposed, into the genome. Such 'retrogenes' are common in humans and *Drosophila*, where they may give rise to new functions. Much less is known about retroposed genes in the budding yeast *Saccharomyces cerevisiae*, another popular genetic model. Joan Curcio (Wadsworth Center, Albany, USA) reported that the biochemical machinery of the long terminal repeat (LTR) retrotransposon Ty1 of yeast can also mediate the reverse transcription of cellular mRNAs, especially when these are at high concentration in the cell. She described how the products of reverse transcription are occasionally integrated back into the genome by homologous recombination with the parental gene. Intriguingly, such replacement of genes by reverse-transcribed copies could offer a credible pathway for the massive loss of introns in the genes of *S. cerevisiae*.

Transposable elements, and other 'selfish' genetic elements that do not benefit the organism, must propagate themselves within the genome in order to avoid extinction in future generations. But the fact that enzymes encoded by transposable elements can act on templates other than their own must pose a major challenge to the survival of selfish elements, as it will impair their own propagation. To avoid being 'parasitized' in this way, human LINE-1 retrotransposons have evolved *cis*-preference, a mechanism by which their enzymatic functions are preferentially directed to their own replicative transposition. This property had been previously observed from genetic evidence, but John Moran (University of Michigan, Ann Arbor, USA) presented the first biochemical evidence for the overwhelming preference of the LINE-1 reverse transcriptase for its own cognate mRNA over any of the highly transcribed cellular mRNAs examined. The mechanism of *cis*-preference is far from perfect, however, as there are at least twice as many parasites of LINE-1 (that is, *Alu*, *SVA*, and retrogenes) than LINE-1 elements themselves in the human genome.

Dynamics of transposable elements in natural populations: a tale of three species

Complete genome sequences provide opportunities to explore the dynamics and compare the activity of large sets of transposable elements in natural populations, aspects of the transposable element biology that remain poorly understood. Haig Kazazian (University of Pennsylvania School of Medicine, Philadelphia, USA) reported that humans of diverse geographic origins display dramatic variation in the relative activity of certain 'hot' LINE-1 elements (that is, elements that are transpositionally very active as assayed in cell culture) and suggested that this variation could contribute to human genetic diversity.

Some transposons move through DNA intermediates rather than RNA, and these can be hot too (that is, highly active). Susan Wessler (University of Georgia, Athens, USA) showed that a single family of miniature inverted-repeat transposable

elements (MITEs) called *mPing* has become amplified to drastically different levels in closely related rice strains (from around 50 to more than 1,000 copies) over just the past few thousand years. This invasion is still going on, and Wessler presented evidence that it is made possible by the rapid elimination of *mPing* copies that land within the coding region of genes, whereas the majority of the remaining insertions - despite being in close proximity to genes - probably have a neutral effect on the host. Perhaps a key to the success of these elements is their small size and the fact that they do not carry either coding or regulatory sequences.

Taking the population genomics of transposable elements to the next level, Dmitri Petrov (Stanford University, Stanford, USA) presented the frequency distribution of around 950 transposable element copies in 72 natural strains of *Drosophila melanogaster*. As with *mPing* in rice, the *Drosophila* study indicates that the majority of insertions are deleterious and are rapidly eliminated from the population, and that the elements that remain in the genome are generally neutral. Petrov also showed, however, that the strength of natural selection against individual copies differs among different transposable element families and, in the case of non-LTR retrotransposons, can be positively correlated to the size of the elements. A possible explanation for this result is that longer elements are more likely to trigger illegitimate recombination events and provoke deleterious chromosomal rearrangements. Together, Petrov's data suggest that illegitimate recombination between homologous transposable element sequences is a major force limiting their proliferation in *D. melanogaster*. Hence, for both rice and fly transposable elements, size does matter.

Taming transposons

Transposable elements have a tumultuous yet long-term relationship with their host. In response to this permanent menace, the host has evolved a variety of taming mechanisms. Alain Bucheton (CNRS, Montpellier, France) showed that suppression of transposition of the *gypsy* retroelement in *Drosophila* involves an RNA-silencing mechanism. In fact, some believe that the widespread RNA-silencing pathways originate from an ancestral immune system aimed at transposable elements, viruses and other intracellular invaders.

Harmit Malik (Fred Hutchinson Cancer Research Center, Seattle, USA) presented the results of elegant evolutionary sequence analyses showing that a short motif in the TRIM5 α protein of primates is responsible for restricting activity of the human immunodeficiency virus HIV-1 in several primate species. He reported that TRIM5 α and members of the APOBEC gene family, also known to restrict retroviral infection, have been rapidly diverging in response to recurrent episodes of positive selection during primate evolution. Malik argued that these results reflect the existence of an ancient intrinsic immune system that has emerged to fight not

only infectious retroviruses, but also endogenous retroelements. Consistent with this prediction, Heide Muckenfuss and her colleague Gerald Schumann (in a poster; Paul Ehrlich Institute, Langen, Germany), reported evidence that APOBEC proteins repress human L1 retrotransposons.

Moving targets

While the host evolves means to combat invasive DNAs, these parasitic elements have in turn evolved smart strategies to minimize the deleterious effects on their host and become less visible to the action of natural selection. Targeting integration to 'safe' genomic havens that contain no or few genes is one strategy; this is seen in the yeast LTR transposons, which preferentially integrate in the gene-poor region upstream of genes transcribed by RNA polymerase III (Ty1 and Ty3) or in silent heterochromatin (Ty5).

According to Dan Voytas (University of Iowa, Ames, USA), targeted integration is a widespread strategy that facilitates the survival of many plant and fungal retrotransposons. He proposed that the accumulation of many retroelements in specific and seemingly less sensitive chromatin compartments of the genome is determined by targeting domains on retroelement proteins that are recurrently acquired throughout the course of their evolution. Voytas presented new results supporting this hypothesis, showing that the chromodomain, a protein domain found at the carboxy terminus of various retrotransposon integrases, is likely to be involved in the preferential accumulation of *Maggy* elements in heterochromatic gene-poor regions of the genome of the fungus *Magnaporthe grisea* and in the localization of CR retrotransposons at the centromere in grasses.

As close cousins of the LTR retrotransposons, retroviruses have also developed tactics to insert into genomic neighborhoods that favor their survival. Frederic Bushman (University of Pennsylvania, Philadelphia, USA) reported that different retroviruses (HIV; murine lymphoma virus, MLV; and avian sarcoma and leukosis virus, ASLV) have unique site preferences for chromosomal integration. In the case of HIV, integration occurs preferentially within active transcription units through a mechanism influenced by the transcription factor LEDGF. In this case, targeting seems to benefit only the invader and not its host, because it may provide a greater chance of the integrated provirus being transcribed and thus the virus being replicated.

Inteins are selfish peptides that insert in-frame within coding regions and are precisely spliced out after translation by their own encoded enzyme. They may represent an extreme example of parasitic targeting strategy. Although these elements were once considered oddities of a few bacterial and yeast genomes, Russell Poulter (University of Otago, New Zealand) and colleagues have taken advantage of the many fungal genome projects and found inteins in a wide

range of fungi. Many more inteins probably await discovery in other eukaryotic genomes.

Transposable elements co-opted

As with other host-parasite systems, the promiscuity and long-term coevolution of transposable elements with the host genome is expected occasionally to give rise to a symbiotic relationship. This is best exemplified by the *HeT-A* and *TART* retrotransposons of *D. melanogaster*, which integrate exclusively at the tips of the chromosomes, where they help maintain the telomeres; the transposition of these elements has become essential for genomic integrity and survival in this species. Elena Casacuberta (IBMB-CSIC, Barcelona, Spain) presented compelling evidence that elements, related to *HeT-A* and *TART*, are also found at the telomeres of *Drosophila yakuba*, *Drosophila pseudobscura* and *Drosophila virilis*, suggesting that a durable relationship between retrotransposons and telomeres was established before the divergence of the *Drosophila* species, some 65 million years ago.

Sometimes, the enzymatic capabilities of transposable elements may be completely usurped to the host's benefit in a process often referred to as 'molecular domestication'. An evolutionarily recent instance of transposable element domestication is provided by *SETMAR*, a primate-specific gene that arose by fusion of a histone methyltransferase SET domain with a *mariner*-like transposase. One of us (C.F.) presented new results indicating that the fusion arose in a common ancestor of anthropoid primates, 40 to 58 million years ago. The function of the *SETMAR* protein is not known but both Zoltan Ivics (Max Delbrück Center, Berlin, Germany) and one of us (C.F.) presented biochemical evidence that the transposase region of *SETMAR* has preserved its ancestral DNA binding activity, while Ron Chalmers (University of Oxford, UK) reported that it has some residual catalytic transpositional capabilities. One of us (C.F.) argued that the DNA-binding activity of the transposase had been recycled to tether the SET domain to multiple chromosomal sites dispersed in the genome as a result of the past amplification of the transposon. In this model a dead transposon family is reincarnated into a regulatory network, an extension of a scenario proposed by Roy Britten and Eric Davidson some 35 years ago.

Another remarkable story of transposable element domestication was told by Jeffrey Miller (University of California School of Medicine, Los Angeles, USA). He described a new group of elements, aptly named diversity-generating retroelements (DGRs), that have been coopted by temperate bacteriophages to bypass the defenses of their bacterial host *Bordetella*. Miller showed that the ability of the phages to infect a new host cell relies on an exchange of genetic information between two direct repeats mediated by a DGR-encoded reverse transcriptase. The process shares similarity

with the transposition mechanism of eukaryotic non-LTR retrotransposons, and it is likely that the direct repeats and source of reverse transcriptase are both derived from the same DGR element that once integrated into the phage genome. DGRs were identified in other phages and in the genomes of some pathogenic bacteria where they also appear to promote the diversification of proteins that are crucial for infection.

The selfish, parasitic and ancient nature of transposable elements has led to their engagement in a coevolutionary relationship with their host. This complex interaction has a dramatic effect on the way genes and genomes evolve. The conference reaffirmed that studying transposable elements in the context of their genomic environment is central to our understanding of the biology and evolution of species, and that research in this field is flourishing in the post-genomic era.