Meeting report

Survival strategies for transposons and genomes

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A report on the Keystone Symposium “Transposition and other genome rearrangements”, Santa Fe, USA, 8-14 February 2003.

The Keystone Symposium “Transposition and other genome rearrangements” covered every level of genome dynamics. The topics ranged from the mechanistic details of transposition and site-specific recombination at the atomic level, through to interactions between transposable elements and the genomes in which they reside that enhance, prevent or control transposon movement, and on to the recognition and classification of novel mobile elements. Recently released genome sequences of human, mouse, mosquito, Chlamydomonas, rice, and fission yeast provided a rich context for a lively and informative meeting. Here, we highlight the presentations that are of special interest to the readership of Genome Biology, as they emphasized how transposable elements and their hosts interact in the ‘genomic ecosystem’ (Figure 1).

Transposons often persist in genomes over millions of years. This requires an exquisite balance between replication and suppression of their activity. The mechanisms used to achieve this balance are as unique and varied as the mechanisms of transposition, which may be either DNA-based (classical transposition) or RNA-based (retrotransposition). Retrotransposons have been particularly successful in eukaryotic genomes, and this success may - as suggested by Jef Boeke (Johns Hopkins University School of Medicine, Baltimore, USA) in his keynote address - reflect enhanced persistence in eukaryotes of the RNA intermediates necessary for reverse transcription. New elements of all classes can be identified in genomic sequences because they occur in multiple copies throughout the genome and on the basis of stereotypic sequence features, such as short target-site duplications, longer direct or inverted repeats, and protein-coding sequences identifiable as transposase or reverse transcriptase.

Not all elements are equally successful in all genomes. For example, in maize retrotransposons comprise 70% of the genome, compared to only 20% in rice. In plants, retrotransposons tend to be found away from genes, whereas DNA transposons, particularly the non-autonomous DNA transposons known as miniature inverted-repeat transposable elements (MITEs) are found in the noncoding regions of genes. Comparative genome analysis between two strains of rice allowed identification of the first active MITE and the transposase required for MITE transposition; the MITE was then shown to transpose in plant cells (Susan Wessler, University of Georgia, Athens, USA). Although retrotransposons that have long terminal repeats (LTRs), so-called LTR-retrotransposons, appear to be inactive in humans, they are quite active in mice. Dixie Mager (University of British Columbia, Vancouver, Canada) provided sequence analysis to support a conclusion that the MusD element is the likely source of the enzymes needed to mobilize the non-autonomous LTR-retrotransposon EtnII, which is frequently responsible for new insertion mutations in mice. In mosquito, non-LTR retrotransposons comprise 3% of the genome, and these are divided into 15 distinct groups (Zhijian Tu, Virginia Technical Institute and State University, Blacksburg, USA). In contrast, a single class of non-LTR elements, L1, comprises 17% of the human genome. Haig Kazazian (University of Pennsylvania, Philadelphia, USA) reported 48 active L1 elements among 90 full-length human elements tested for transposition activity, with six ‘hot’ elements accounting for 84% of the total activity. L1 is a repeated sequence that occurs in high copy numbers in all mammalian genomes, but not all species currently have active L1 elements. As reported on a poster by Holly Wichman (University of Idaho, Moscow, USA), there
have been at least three separate extinctions of L1 during mammalian evolution.

What mechanisms suppress transposition? Ronald Plasterk (Netherlands Institute for Developmental Biology, Utrecht, The Netherlands) suggested that RNA-mediated interference (RNAi) is a genome-based defense against repeated DNA, such as transposons. Exhaustive genetic screens in Caenorhabditis elegans uncovered many mutations that stimulate germline transposition of the Tc1 element and blunt or abolish RNAi; furthermore, double-stranded Tc1 transcripts trigger RNAi. The effects of RNAi on transposon silencing occur both pre- and post-transcriptionally. On the transcriptional front, Heriberto Cerutti (University of Nebraska, Lincoln, USA) presented evidence linking RNAi with epigenetic transcriptional silencing of transposons in Chlamydomonas by using histone modification to create repressive chromatin at double-strand break sites in DNA. Damon Lisch and colleagues (University of California, Berkeley, USA) have identified two genes, Mu Killer and mop1, that heritably methylate and silence, or demethylate and reactivate, the Mutator DNA transposon in maize, respectively. Reinhard Kunze (University of Cologne, Germany) presented data suggesting that the maize element Ac escapes methylation-mediated repression during replication when transposon DNA is hemi-methylated. But the mechanism he described seems to act on the transposon ends to control excision, perhaps involving the emerging relationship between heterochromatin formation and RNAi. Meng-Chao Yao (Fred Hutchinson Cancer Research Center, Seattle, USA) presented data indicating that RNAi-mediated defense mechanisms extend beyond pre- and post-transcriptional gene silencing to the programmed DNA rearrangements in the Tetrahymena macronucleus, where invading DNA is deleted, whether in a single copy or many. Budding yeast, although lacking the evolutionarily conserved RNAi pathway, nevertheless controls transposon activity by a novel form of post-transcriptional copy number control or co-suppression. In the case of the Ty1 element, genome-length RNA transcripts increase with copy number but are poorly utilized for retrotransposition, perhaps because Ty1 RNA is sequestered
from translation or reverse transcription (D.G.). Transposon-encoded proteins may also be directly targeted to reduce transposition activity; Donald Rio (University of California, Berkeley, USA) reported negative regulation of P-element excision in Drosophila by transposase phosphorylation.

Perhaps it is no accident that transposition often appears intrinsically inefficient compared to other cellular processes. Boeke provided evidence for poor transcriptional elongation through the ORF2 domain of human L1, and Prescott Deininger (Tulane University, New Orleans, USA) presented a poster indicating that premature polyadenylation and instability of L1 RNA also limit accumulation of the full-length RNA retrotransposition intermediate. Thomas Eickbush (University of Rochester, USA) reported that the nucleolar Drosophila R2 element, which is embedded in 28S rDNA, is co-transcribed with the ribosomal RNA. This chimeric rRNA is assembled into 50S ribosomal subunits, making cap-dependent translation of the R2 protein problematic. Furthermore, Henry Levin (National Institute of Child Health and Human Development, National Institutes of Health (NIH), Bethesda, USA) provided evidence suggesting that reverse transcription of the wild-type Tf1 element produces many cDNA molecules with defective 3' ends in fission yeast.

Transposons have also evolved special relationships with host factors to minimize the impact of transposition. 'Cut-and-paste' transposons leave a double-stranded DNA break in the donor chromosome that must be repaired for cells to remain viable. Drosophila has solved this problem for P-element-mediated excision events in the germline by utilizing double-strand break repair pathways, such as non-homologous end joining or homologous recombination, as reported by Rio and William Engel (University of Wisconsin, Madison, USA). Zsuzsanna Izsák (Max Delbrück Center for Molecular Medicine, Berlin, Germany) provided evidence that healing of 'wounds' in the mammalian genome caused by excision of the Tcl-like element Sleeping Beauty requires several proteins involved in non-homologous end joining as well as the protein kinase ATM. A genome-wide screen for reduced retrotransposition of Ty1 showed that many host genes in budding yeast, including several genes involved in DNA repair, facilitate retrotransposition (Scott Devine, Emory University School of Medicine, Atlanta, USA). Finally, transposons often have specific targeting mechanisms that exploit 'safe havens' in the genome, such as noncoding or transcriptionally repressed regions. For example, Levin provided compelling evidence that the Tf1 integration machinery recognizes histone modifications present in the 5' non-coding regions of fission yeast genes, and Daniel Voytas (Iowa State University, Ames, USA) showed that targeting of the yeast Ty5 element to silent chromatin involves relatively simple protein-protein interactions that are sufficient to specify 'designer' insertion sites.

Some transposons can clearly be regarded as beneficial to their genome. Two interdependent retrotransposons, HeT-A and TART, form the telomeres in diverse Drosophila species and provide an unusual mechanism of telomere maintenance that seems to have been in place for at least the past 60 million years (Mary-Lou Pardue, Massachusetts Institute of Technology, Cambridge, USA). The adaptive immune response is widely believed to be derived from a harnessed transposon on the basis of similarities in the reactions catalyzed by transposases and the Rag proteins, which are involved in the rearrangement of T-cell receptor and immunoglobulin genes (Martin Gellert, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, USA). Working with the hypothesis that the progenitor transposon should have recognizable features, such as the end-recognition sequences for Rag-mediated recombination, but should lie outside the immunoglobulin or T-cell receptor loci, Lindsey Cowell (Duke University, Durham, USA) reported a computational approach that allowed the recognition of these features and provided examples that are in both the mouse and the human genomes. A gene with unknown function (Eeyore) that has the unmistakable sequence features of a functional gene is derived from the Tigger1 transposase and is found in all primates (Hugh Robertson, University of Illinois at Champagne-Urbana, USA). Finally, transposons may come to the rescue under conditions that cause genomic stress. M. Joan Curcio (Wadsworth Center, Albany, USA) reported that survival of yeast cells after the loss of telomerase can occur by amplification of subtelomeric Y' sequences on chromosome ends via a mechanism involving Ty1, and John Moran (University of Michigan, Ann Arbor, USA) reported that atypical L1 insertions are found in mammalian cells that are defective for the non-homologous end-joining machinery; the sequences of these insertions suggest that L1 can patch double-strand DNA breaks by using a mechanism similar to the one mediated by telomerase.

Genome research benefits when transposons are understood well enough to harness as tools. Alan Lambowitz (University of Texas, Austin, USA) described an algorithm to design type II introns that can target any gene, and he demonstrated its utility by disrupting all the genes encoding DEAD-box proteins in Escherichia coli. Koichi Kawakami (National Institute of Genetics, Shizuoka, Japan) developed a modified Tol2 element that can be used as a promoter- and gene-trap system in zebrafish and showed that it also works in frog and mouse embryonic stem cells. Thomas Peterson (Iowa State University, Ames, USA) suggested that the Ac/Ds transposon system of maize could be exploited to create large deletions in chromosomes to facilitate gene mapping.

In summary, the 2003 symposium showed that steady progress has been made in all areas of transposon biology, with some particularly provocative advances. As expected from a successful conference, many new and intriguing questions were raised regarding the interactions between transposons and the genomes in which they are located. Look for advances in this area to steal the limelight next time this group convenes.