On being the right size

Edward C Holmes

The first replicating molecules were probably composed of RNA and undoubtedly small, limited in size by a self-destructing error rate. A new study shows that a relatively minor increase in replication fidelity may have had a large effect on the size, and hence complexity, of early replicators.

A distinctive feature of RNA molecules is that they generally form complex secondary structures, complete with loops, hairpins and bulges. This is central to understanding the evolution of early replicators, because such structures, and the complex fitness landscapes they enforce, means that many of the mutations that arise either will be neutral, and hence have no effect on fitness, or will interact epistatically. In sum, the effect of RNA secondary structure is to remove the one-to-one relationship between genotype and phenotype, producing what Kun et al. call a relaxed error threshold3, buffering early replicators against mutational meltdown. Crucially, if the fitness landscapes of present-day ribozymes can be calculated, as Kun et al. attempt to do4, then it should also be possible to estimate, albeit roughly, what sizes early RNA replicators would have been able to achieve under given mutation rates. As raw data, Kun et al. examined the fitness landscapes of two small ribozymes, the hairpin and Neurospora VS ribozymes3. The secondary structures of these ribozymes can be predicted, and extensive mutagenesis studies can be used to estimate fitness. Fitting data to model suggested that a decrease in the error rate from 0.1–0.01 to 0.001 mutations per nucleotide per replication would result in many replicators in the size range of 7–8 kb, equivalent to that of contemporary tRNAs and RNA viruses (Fig. 1).

From RNA to DNA

Despite the results of Kun et al.3, some key questions remain unanswered. In particular, although an increase in replicator size from several hundred nucleotides to >7 kb represents a large enhancement of genetic complexity and is undoubtedly sufficient for an RNA world, it is very much smaller than either the tiniest cellular life forms known today or the estimated size of the genome of the last universal common ancestor5. More fundamentally, the most abundant RNA life forms, RNA viruses, usually have genomes <12 kb in length. Hence, although most RNA viruses are larger and more complex than ribozymes and have greater copying fidelity, they are also at the mercy of an error threshold (Fig. 1). This

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Figure 1 Error thresholds and the origin of life. For evolution to proceed in the RNA world, a reduction in the error rate (µ) to ~0.001 mutations per nucleotide per replication must be achieved. For more complex genomes to evolve, with sizes >10^4 nucleotides, a second threshold needs to be crossed in which µ << 0.001. This necessitates the evolution of DNA replication, which provides a higher copying fidelity than RNA. Neutral and compensatory changes tend to dampen the effects of deleterious mutations, allowing a relaxed error threshold. In contrast, antiviral drugs that increase the error rate tend to push contemporary RNA viruses over the error threshold and into lethal mutagenesis.
Elucidating mouse transmission ratio distortion

Mary F Lyon

A proportion of wild mice carry a variant region of chromosome 17 that results in severe transmission ratio distortion in males. The genetic basis of this distortion has long been enigmatic, but a recent study begins to disentangle it.

On page 969 of this issue, Bernhard Herrmann and colleagues report the cloning of a distorter gene in the transmission ratio distortion system of the mouse t complex.1 Why is this so exciting? The t complex has been baffling geneticists for more than 70 years. It is a variant form of the proximal region of chromosome 17 found in a proportion of wild mice. Male mice heterozygous with respect to a t haplotype (as the variant forms are called) transmit it to an abnormally high proportion of their young, up to 99%. Males carrying two t haplotypes are sterile. Females show normal transmission and fertility. The t complex occupies roughly one-third of chromosome 17 but is inherited as a unit, owing to strong crossover suppression caused by four nonoverlapping inversions (Fig. 1). Study of rare crossovers that give rise to partial haplotypes has shown that the transmission ratio distortion depends on the action of several factors located in or between the inversions. The current view is that there are three or more distorters, Tcd1–Tcd3, that act on a responder, Tcr.2 The distorters have a harmful effect and act on any chromosome, but the t form of the responder, Tcr,3 is resistant to this effect and acts only in cis. Thus, sperm carrying Tcr are protected from the harmful distorters and are able to fertilize eggs, giving rise to the ratio distortion. The distorters are postulated to act cumulatively, and when they are homozygous, the resistance of Tcr is overcome so that no sperm can fertilize eggs, and sterility results. The sperm are not killed, but their swimming is much impaired and few reach the oviduct (Fig. 1).

A key obstacle to cloning the responder and distorters is that there are too few individuals to be studied.4 The responder was recently cloned by Bernhard Herrmann and colleagues5, who found in the appropriate region a hybrid gene, formed by the fusion of two kinases. The 5′ end of a ribosome S6 kinase was fused to a previously unknown kinase related to the microtubule-associated protein family, called Smok1-GAP domain.6 The fused gene was called Smok1-Tcr.7 When this gene was introduced as a transgene at a random location, if a partial t haplotype with distorters was also present, then the chromosome carrying Tcr was transmitted at a high ratio. Thus, Tcr showed behavior typical of the responder, and Herrmann and colleagues concluded that it was the responder. They considered Tcr to be part of a signaling cascade and surmised that the distorters acted upstream of Tcr in this cascade.

Search for distorters

They began a search for distorters in the region in which Tcd1 was postulated to lie and isolated a gene called T-cell activation Rho GTPase-activating protein, Tagap1, which differed between t and wild-type strains. The t haplotypes carried four Tagap1 loci, whereas the wild type carried only one. The t haplotype cDNAs showed several nucleotide differences from wild-type, including one that resulted in a truncated protein with an intact N-terminal RhoGAP domain. Tagap1 is transcribed in the testes and at a higher level in t haplotypes than in the wild type.

Thus, Tagap1 fulfilled two necessary criteria for a distortor gene: it was expressed in the testes and differed between t haplotypes and the wild type. The crucial question was whether it affected ratio distortion. In view of the higher expression of the t form of Tagap1, Herrmann and colleagues assessed the effect of overexpressing the wild-type allele by means of a transgene. They compared the transmission ratio of a haplotype lacking Tcd1 in males with and without the transgene, and males with the transgene had a higher ratio (Fig. 1). Conversely, Tagap1-knockout males had significantly reduced transmission. This means that Tagap1 possesses the essential property of distorting the transmission of a 1 t haplotype and fulfills the criteria to be considered the first distorter gene to be identified in the t complex. It also fits with Herrmann’s earlier prediction that the distorters would act upstream of Smok1 in a signaling cascade. The effect of the cascade on microtubule function could affect flagellar movements. Thus, at long last we have a picture of the mechanism of transmission ratio distortion in the t complex.

Puzzles and questions

But this is not the end of the story. Tagap1 in its distortor role acts as a hypermorph.