

## The recombination–replication interface

The ‘three R’s’ of genome manipulation – DNA replication, recombination and repair – have long been considered to be largely separate biological processes and have been studied generally by separate groups of investigators. The study of replication has traditionally dealt with the biochemical ‘nuts and bolts’ of the template-directed polymerization whereby genomic DNA is ‘copied’ during cell division. This process involves some transient DNA ‘editing’ (repair), courtesy of the 3’→5’ exonuclease activity that is part of most replication polymerases. But once left behind by the replication complex, the remaining errors became the province of a completely different group of enzymes and researchers focused on the processes and mechanisms of DNA lesion excision and repair. In contrast to both of these fields, which have tended to be studied primarily by biochemists and enzymologists, DNA recombination was viewed as a much more elegant and esoteric biological process that mixed genes and drove evolution, and was studied mostly by geneticists.

This separation of science and scientists began to break down when investigators of DNA repair pathways showed that after DNA lesions had been recognized and excised, significant template-directed DNA replication was required to resynthesize the missing sequences. Furthermore, recombination components seemed to be required to permit proper realignment of templates in this sequence maintenance and rebuilding process, as

evidenced by genetic observations that showed that UV-induced lesions were often not successfully repaired in recombination-deficient mutants.

The full integration of replication and recombination took longer, although Anne Skalka (in bacteriophage  $\lambda$ ), Gisela Mosig (in bacteriophage T4) and Tokio Kogoma (in *E. coli*) recognized some years ago that recombination mechanisms could be very important in restarting (‘rescuing’) replication complexes that had encountered lesions and become stuck, or had otherwise ‘fallen apart’ (for Refs, see overview by S. Kowalczykowski in this issue of *TiBS*). However, the universality of their observations were not recognized until very recently, partly because the rigidity of the division into the three R’s took time to break down, and partly because interpretation of their observations required a new, integrated way of thinking.

In retrospect, of course, it seems obvious that ‘errors’ in replication must occur at the level of the whole replication fork, as well as at the single base pair level of the DNA sequence, and that the sophisticated interplay between all three R’s would be required to keep cells viable in the successful completion of even a single cycle of replication. Thus another way of looking at the processes of gene mixing and accelerated evolution that are driven by recombination is that these processes actually represent the accumulated consequences of the rescue of many derelict replication forks in each cycle of DNA synthesis, rather than the effects of a more cosmic plan for reshuffling the genome.

These realizations are new, and our understanding of the details is still limited. However, this is a field that is now moving fast, that is largely unknown to the greater biochemical community, and that has widespread consequences for processes ranging from replication fork restarts to telomerase-independent telomere length maintenance. Those of us who have a ‘prokaryotic perspective’ might not be able to refrain from pointing out, as the articles in this Special Issue of *TiBS* make clear, that the recombination–replication interface represents yet another area where much of the understanding of eukaryotic systems has been derived from earlier studies of bacteria and phage.

The ubiquity of these new intersections of the replication, recombination and repair fields, and the emerging importance of these ideas in so many areas of genome synthesis and gene expression, convinced the Editors that these developments represented an appropriate and timely topic for a Special Issue of *TiBS*. We were pleased to see these impressions validated by the enthusiastic response that we met from the authors, and by the integrated insights of the articles that they have contributed. Although it is clear that our understanding of this area is far from complete, we hope that the articles presented here will serve both to stimulate further work in the field and to attract new investigators who previously might not have appreciated the power of this way of looking at many of the central issues of genome perpetuation and expression.

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### Tokio Kogoma (1939–1997)

The editors wish to honor the memory of Tokio Kogoma, who contributed significantly to the inception of this field and who died in October 1997. To this end we have asked David Bear, who was a long-time colleague of Tokio Kogoma at the University of New Mexico, to write a short memoir. David has contributed the following.

‘Tok was deeply interested in the interplay between DNA replication, recombination and transcription. During the early stages of his career as a post-doctoral fellow with Gordon Lark – when he published his first paper on stable DNA replication (SDR) in 1970 – and later as a faculty member at the University of New Mexico, Tok characterized a series of *E. coli* mutants that could carry out DNA replication in the absence of protein synthesis. This alternative replication mode was first viewed by the bacterial molecular biology community as little more than a minor pathway to ensure cell survival under highly unlikely circumstances. At conferences, many of Tok’s colleagues often had trouble following his soft-spoken descriptions of complicated bacterial genetic experiments that attempted to link SDR with other facets of bacterial physiology. Nevertheless, through a combination of perseverance and very clever experimental approaches, Tok and his colleagues succeeded in defining the proteins and physiological conditions that are important for SDR. The results demonstrated that SDR involves a number of enzymes essential to DNA recombination and repair. In addition, these studies suggested that the structural nucleic acid intermediates involved in recombination (D-loops) and transcription (R-loops) could also operate as sites of initiation for SDR. In the last few years, before he passed away at an early age from cancer, Tok was able to unify much of his data into elegant models for the role of D-loops and R-loops in alternative DNA replication, and he suggested how these pathways might play a role in eukaryotic organisms. Tok Kogoma promoted the idea, long before it became fashionable, that the biochemical reactions of the genetic apparatus constitute an integrated system, designed to work together within the context of the physiological state of the cell.’

Stephen Kowalczykowski and Peter von Hippel