Am. J. Hum. Genet. 61:18–22, 1997

COMMENTARY
Homologous Recombination in Human Mitochondria?

Human mitochondria are widely thought to lack mechanisms for DNA repair and recombination, but this view may be shifting. Although the classic observation that UV-induced intrastrand pyrimidine dimers accumulate in mtDNA without being repaired has been verified recently, it seems now that this class of DNA lesion is exceptional. Other lesions, in which mtDNA is damaged by exposure to oxidants or to various drugs, are repaired efficiently by mechanisms that are analogous to familiar pathways that operate in cell nuclei. Many of the enzymatic activities required for DNA metabolism—endonucleases, uracil DNA glycosylase, and topoisomerases, among others—are found in both nuclear and mitochondrial extracts.

In last November's *Journal of Biological Chemistry,* Thyagarajan et al. added another activity to this list, that of a DNA recombinase. Using a mitochondrial extract and a pair of plasmids with distinct deletions in a selectable marker gene, this group showed that a mitochondrial protein related to RecA, the major recombinase from *E. coli,* can catalyze homologous recombination (HR) in vitro. This mitochondrial activity is similar to that of Rad51, the mammalian nuclear counterpart of RecA, but, on biochemical grounds, the nuclear and mitochondrial activities can be distinguished.

A long history of negative findings argues that HR in human mtDNA is either rare or nonexistent. Cell-fusion experiments, with, for example, mouse/human cybrids, have failed to detect HR, but there are trivial explanations that make it difficult to interpret such results. For instance, the assumption that mtDNAs mix efficiently within a given cell is controversial. Colin Campbell, the principal author of the paper in the *Journal of Biological Chemistry,* argues that human mitochondria might lack HR, but that, if they do, they are unusual: Other plastid chromosomes, such as yeast mitochondria, as well as chloroplasts and mitochondria from various plants, do undergo genetic exchange via HR. Even in these genomes, however, HR is observed best when transgenic plastids are made, a technique that has not yet been applied successfully to mammalian mitochondria. Once a method as sensitive as this is available, it should be possible to address the issue of genetic exchange in vivo. Even without such data, however, the activity seen in vitro is provocative.

If mtDNA undergoes HR in vivo, even at a low level, human geneticists may find themselves reexamining several common assumptions. In the study of human origins, for example, mtDNA sequence variation provides much of the data used to reconstruct the history of populations, and mtDNA sequence changes are assumed to accumulate at a steady rate. The existence of a mitochondrial recombinase, whether it leads to shuffling of mtDNA sequences or whether it serves as part of an mtDNA repair system, could well complicate the analysis. Population geneticist Rebecca Cann suggests that gene conversion in mtDNA may lead to concerted evolution of mtDNA sequences, much as sequences of nuclear genes in multigene families evolve together, rather than diverging from each other at the expected rate. To the extent that mtDNA populations become homogenized by recombination, the evolutionary history of an mtDNA sequence will approximate that of a single-copy gene. In this view, HR could function to suppress heteroplasmy, just as bottlenecks in mtDNA transmission are assumed to do. Hence, according to Cann, HR need not necessarily create a novel problem for the population geneticist. However, if mtDNA recombination and repair are under control of the nuclear genome (as appears to be the case in certain families with unstable mitochondrial genomes), then chromosomal loci may well play a part in the rate of mtDNA mutation. It is not clear that current methods for the analysis of human divergence are compatible with a mutation rate that varies within or between populations.

The findings raise other questions: If the activity is observed so readily in vitro, why is genetic recombination observed so rarely? Does a RecA-like enzyme create the mtDNA deletions and expansions that are commonly attributed to inaccurate replication in the slipped-strand model? What else might a recombinase be used for in mitochondria if not for repair or for genetic recombination? In the following essay, Neil Howell addresses each of these questions, setting the stage, perhaps, for a wider discussion of recombination in mitochondrial biology.

JOHN ASHKENAS
Editorial Fellow