Recombination

Recombination lends the genome flexibility. Without genetic recombination, the genes on each individual chromosome would remain fixed in their particular position. Changes could occur by mutation only, which would be hazardous. Recombination provides the means to achieve extensive restructuring, eliminate unfavorable mutation, maintain and spread favorable mutations, and endow each individual with a unique set of genetic information. This greatly enhances the evolutionary potential of the genome. Recombination must occur between precisely corresponding sequences (homologous recombination) to ensure that not one base pair is lost or added. The newly combined (recombined) stretches of DNA must retain their original structure in order to function properly. Two types of recombination can be distinguished: (1) generalized or homologous recombination, which in eukaryotes occurs at meiosis and (2) site-specific recombination. A third process, transposition, utilizes recombination to insert one DNA sequence into another without regard to sequence homology. Here we consider homologous recombination, a complex biochemical reaction between two duplexes of DNA. The necessary enzymes, which can involve any pair of homologous sequences, are not considered. Two general models can be distinguished, recombination initiated from a single-strand DNA break and recombination initiated from a double-strand break.

A. Recombination initiated by single-strand breaks

This model assumes that the process starts with breaks at corresponding positions of one of the strands of homologous DNA (same sequences of different parental origin) (1). A nick is made by a single-strand-breaking enzyme (endonuclease) in

each molecule at the corresponding site (2), but see below. This allows the free ends of one nicked strand to join with the free ends of the other nicked strand, from the other molecule, to form single-strand exchanges between the two duplex molecules at the recombination joint (3). The recombination joint moves along the duplex (branch migration) (4). This is an important feature because it ensures that sufficient distance for the second nick is present in each of the other strands (5). After the two other strands have joined and gaps have been sealed (6), a reciprocal recombinant molecule is generated (7). Recombination involving DNA duplexes requires topological changes, i.e., either the molecules must be free to rotate or the restraint must be relieved in some other way. This model has an unresolved difficulty: How is it assured that the single-strand nicks shown in step 2 occur at precisely the same position in the two double helix DNA molecules?

B. Recombination initiated by double-strand breaks

The current model for recombination is based on initial double-strand breaks in one of the two homologous DNA molecules (1). Both strands are cleaved by an endonuclease, and the break is enlarged to a gap by an exonuclease that removes the new 5′ ends of the strands at the break and leaves 3′ single-stranded ends (2). One free 3′ end recombines with a homologous strand of the other molecule (3). This generates a D loop consisting of a displaced strand from the “donor” duplex. The D loop is extended by repair synthesis until the entire gap of the recipient molecule is closed (4). This displaced strand anneals to the single-stranded complementary homologous sequences of the recipient strand and closes the gap (5). DNA repair synthesis from the other 3′ end closes the remaining gap (6). The integrity of the two molecules is restored by two rounds of single strand repair synthesis. In

contrast to the single-strand exchange model, the double strand breaks result in hetero-duplex DNA in the entire region that has undergone recombination. An apparent disadvantage is the temporary loss of information in the gaps after the initial cleavage. However, the ability to retrieve this information by resynthesis from the other duplex avoids permanent loss.