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Mini-review

Regulation of DNA strand exchange in homologous recombination

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ABSTRACT

Homologous recombination, the exchange of DNA strands between homologous DNA molecules, is involved in repair of many structural diverse DNA lesions. This versatility stems from multiple ways in which homologous DNA strands can be rearranged. At the core of homologous recombination are recombinase proteins such as RecA and RAD51 that mediate homology recognition and DNA strand exchange through formation of a dynamic nucleoprotein filament. Four stages in the life cycle of nucleoprotein filaments are filament nucleation, filament growth, homologous DNA pairing and strand exchange, and filament dissociation. Progression through this cycle requires a sequence of recombinase–DNA and recombinase protein–protein interactions coupled to ATP binding and hydrolysis. The function of recombinases is controlled by accessory proteins that allow coordination of strand exchange with other steps of homologous recombination and that tailor to the needs of specific aberrant DNA structures undergoing recombination. Accessory proteins are also able to reverse filament formation thereby guarding against inappropriate DNA rearrangements. The dynamic instability of the recombinase–DNA interactions allows both positive and negative action of accessory proteins thereby ensuring that genome maintenance by homologous recombination is not only flexible and versatile, but also accurate.

Contents

1. Introduction

Evolution, the fundamental process that drives biological diversity, demands changes in genomic DNA, the carrier of genetic information. In this light the inherent instability of DNA, a molecule subject to spontaneous hydrolysis reactions and attack from chemicals or radiation, is an advantage. Alterations in the chemical structure of DNA can induce mutations that fuel evolution. However, at the level of the individual, a certain degree of genome stability is required to guard against diseases, including cancer. DNA repair reactions that can restore the structure and functionality of damaged DNA provide a balance between evolution and development of disease [1,2]. We focus on one such repair reaction; homologous recombination, the exchange of DNA strands between homologous DNA molecules.

Due to the chemical complexity of DNA numerous structurally diverse lesions can occur. It is therefore not surprising that multiple DNA repair reactions have evolved [1,2]. Decades of genetic and biochemical experiments resulted in the classification of dis-

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tinct repair pathways and the outline of their mechanisms are emerging. Many DNA repair pathways function by pinpointing the offending covalent chemical adduct modifying DNA through a structure-specific DNA binding protein or protein complex. This recognition event triggers a series of subsequent lesion-processing reactions that eventually restore DNA structure to effect repair. Examples of such pathways include base excision repair, nucleotide excision repair and mismatch repair, which are initiated by recognition of the damaged or incorrect deoxynucleotide, followed by its excision and reinsertion of the correct nucleotide(s) using the complementary DNA strand as a template. The advantage of structure recognition to initiate repair is high specificity, but this also inherently limits the diversity of lesions that can be repaired through each pathway. Homologous recombination does not have this limitation since it does not directly recognize DNA lesions. Instead, the process is initiated on the single-stranded form of DNA, which does not need to contain lesions itself, although it could have arisen as a response to DNA lesions [3–5]. This indirect DNA damage recognition mode and the multiple ways to rearrange homologous DNA strands allows great flexibility in applying homologous recombination to repair many structural diverse DNA lesions or alternative DNA structures, including single-strand gaps, double-strand breaks (DSBs) (Fig. 1), interstrand crosslinks and stalled/collapsed replication forks [71–74].

The multiple applications of homologous recombination in DNA repair imply that this process is subject to multiple control mechanisms [6]. In addition, homologous recombination is only a repair mechanism if the DNA rearrangements catalyzed contribute to DNA genomic stability rather than instability. The exchange of base-paired partners between a DNA segment in need of repair and an undamaged duplex partner of homologous sequence is at the core of DNA repair by homologous recombination [7,25]. Control of homologous recombination repair is focused on controlling this strand exchange step. Notably this reaction is absolutely required for error-free repair of damage involving both strand of duplex DNA. To provide context for this central reaction and

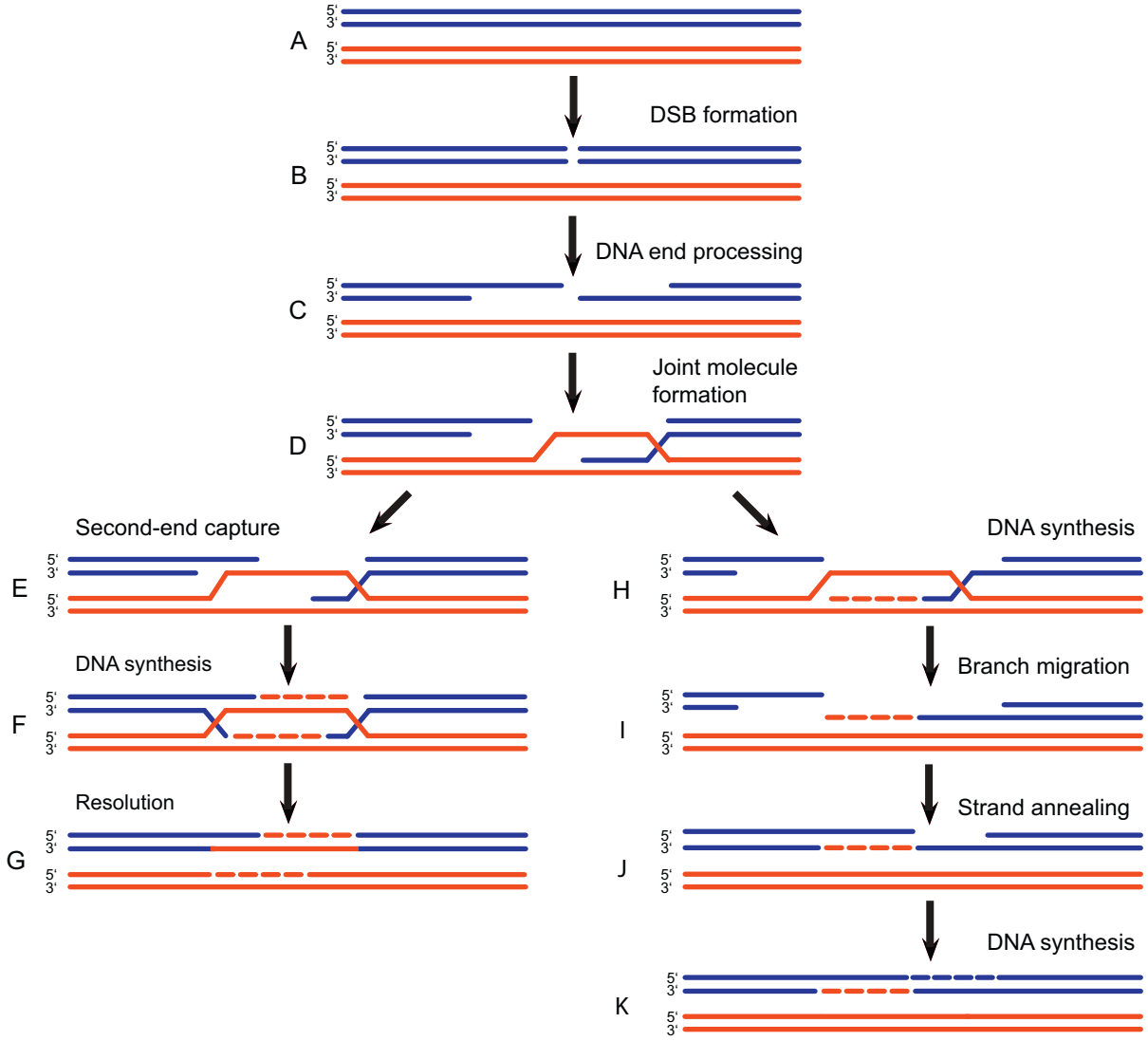

Fig. 1. Schematic representation of a model for DSB-initiated homologous recombination. (A) Two duplex DNAs, representing homologous sister chromatids, are indicated by parallel blue and red lines. This cartoon focuses on the DNA events during recombination and therefore participating proteins are omitted. Upon DSB formation (B), the ends are nucleolytically processed to result in 3′ single-stranded tails (C). (D) Recombinase proteins assembled in a nucleoprotein filament on the single-stranded DNA mediate joint molecule formation between the processed broken DNA and the homologous duplex repair template via homology recognition and DNA strand exchange. Downstream of joint molecule formation, two subpathways of homologous recombination are indicated: DSBR [75] and SDSA [76]. (E) In the DSBR pathway the second DNA end is engaged and upon DNA synthesis, the recombining molecules are joined via Holliday junctions (F). (G) Resolution of the junctions by structure-specific endonucleases releases two repaired duplex DNAs. (H) Upon DNA synthesis in the SDSA pathway the joint molecule is dissolved (I) and the newly synthesized DNA strand anneals with the processed second DNA end (J). Repair DNA synthesis completes repair (K).