Seminars in Cancer Biology 20 (2010) 222–233

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Review

Genomic rearrangements in inherited disease and cancer

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ARTICLE INFO

Keywords:
Cancer
Copy number variation
Genomic rearrangements
Homologous recombination
Non-homologous end joining

ABSTRACT

Genomic rearrangements in inherited disease and cancer involve gross alterations of chromosomes or large chromosomal regions and can take the form of deletions, duplications, insertions, inversions or translocations. The characterization of a considerable number of rearrangement breakpoints has now been accomplished at the nucleotide sequence level, thereby providing an invaluable resource for the detailed study of the mutational mechanisms which underlie genomic recombination events. A better understanding of these mutational mechanisms is vital for improving the design of mutation detection strategies. At least five categories of mutational mechanism are known to give rise to genomic rearrangements: (i) homologous recombination including non-allelic homologous recombination (NAHR), gene conversion, single strand annealing (SSA) and break-induced replication (BIR), (ii) non-homologous end joining (NHEJ), (iii) microhomology-mediated replication-dependent recombination (MMRDR), (iv) long interspersed element-1 (LINE-1 or L1)-mediated retrotransposition and (v) telomere healing. Focussing on the first three of these general mechanisms, we compare and contrast their hallmark characteristics, and discuss the role of various local DNA sequence features (e.g. recombination-promoting motifs, repetitive sequences and sequences capable of non-B DNA formation) in mediating the recombination events that underlie gross genomic rearrangements. Finally, we explore how studies both at the level of the gene (using the neurofibromatosis type-1 gene as an example) and the whole genome (using data derived from cancer genome sequencing studies) are shaping our understanding of the impact of genomic rearrangements as a cause of human genetic disease.

1. Introduction

Genomic rearrangements constitute changes in the genetic linkage relationship of discrete chromosomal fragments and can involve deletions, duplications, insertions, inversions or translocations. Historically, genomic rearrangements have been extensively studied by means of either classical cytogenetic or molecular biological techniques. Only fairly recently has the resolution gap between these techniques been bridged by technological advances. Since two landmark studies six years ago [1,2], genomic rearrangements of intermediate scale—now commonly known as copy number variation (CNV; a ≥1 kb DNA segment that differs in terms of its copy number with respect to a reference genome sequence [3])—have been found in increasing numbers to cause or predispose to human inherited disease and cancer. An increasing number of rearrangement breakpoints have been characterized at the nucleotide sequence level, thereby providing an invaluable resource for the detailed study of mutational mechanisms underlying genomic recombination events. A better understanding of these mutational mechanisms is vital for improving the design of mutation detection strategies. In this article, we shall provide an overview of the mutational mechanisms put forward to account for the diverse range of known genomic rearrangements, with an emphasis on new insights generated from recent

Abbreviations: aCGH, array comparative genomic hybridization; BIR, break-induced replication; CNV, copy number variation; CNM, copy number mutation; D-loop, displacement loop; DSB, double-strand break; FoSTes, fork stalling and template switching; HJ, Holliday junction; LCRs, low copy repeats; LINE-1 or L1, long interspersed element-1; NAHR, non-allelic homologous recombination; NHEJ, non-homologous end joining; MMRDR, microhomology-mediated replication-dependent recombination; ROHs, runs of homozygosity; SRS, serial replication slippage; SSA, single-strand annealing; ssDNA, single-stranded DNA.

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doi:10.1016/j.semcancer.2010.05.007

studies of both inherited disease and cancer, and highlight the most significant findings obtained from cancer genome sequencing studies.

2. Mutational mechanisms of genomic rearrangement

At least five categories of mutational mechanism can give rise to genomic rearrangements: homologous recombination, non-homologous end joining (NHEJ), microhomology-mediated replication-dependent recombination (MMRDR), long interspersed element-1 (LINE-1 or L1)-mediated retrotransposition, and telomere healing. The latter two can perhaps be described as specialized mechanisms as compared with the first three. L1-dependent retrotransposition is thought to occur by target site-primed reverse transcription. Besides simple self-insertion, L1 elements can mobilize their 5′- and 3′-flanking DNA sequences *in cis* and non-autonomous sequences *in trans* (e.g. *Alu* sequences) to new genomic locations. Moreover, L1 retrotransposition can also give rise to large genomic deletions (for reviews, see [4–6]). Telomere healing refers to a process during which the end of a broken chromosome is stabilized by the telomerase-dependent addition of telomeres at non-telomeric sites (reviewed in [7]). In this section, we shall focus on the first three general mechanisms. We shall attempt to compare and contrast their characteristic hallmarks, emphasize new developments, and discuss the role of various local DNA sequence features in mediating gross genomic rearrangements.

2.1. Homologous recombination

Homologous recombination is one of the major pathways for the repair of double-strand breaks (DSBs). As the term implies, it is mediated through sequences which exhibit considerable homology (generally >200 bp) that presumably serves to stabilize chromosomal mispairing. Homologous recombination is upregulated in the S and G2 phases of the cell cycle, when sister chromatids are readily available. It can be further sub-divided into four pathways, namely, non-allelic homologous recombination (NAHR), gene conversion, break-induced replication (BIR) and single-strand annealing (SSA) (Fig. 1). These pathways share similar initiating events: the DSB generated within one of the duplicated or repeated sequences undergoes extensive 5′-end resection to form 3′ single-stranded DNA (ssDNA) tails; these tails, once coated with the Rad51 recombi-

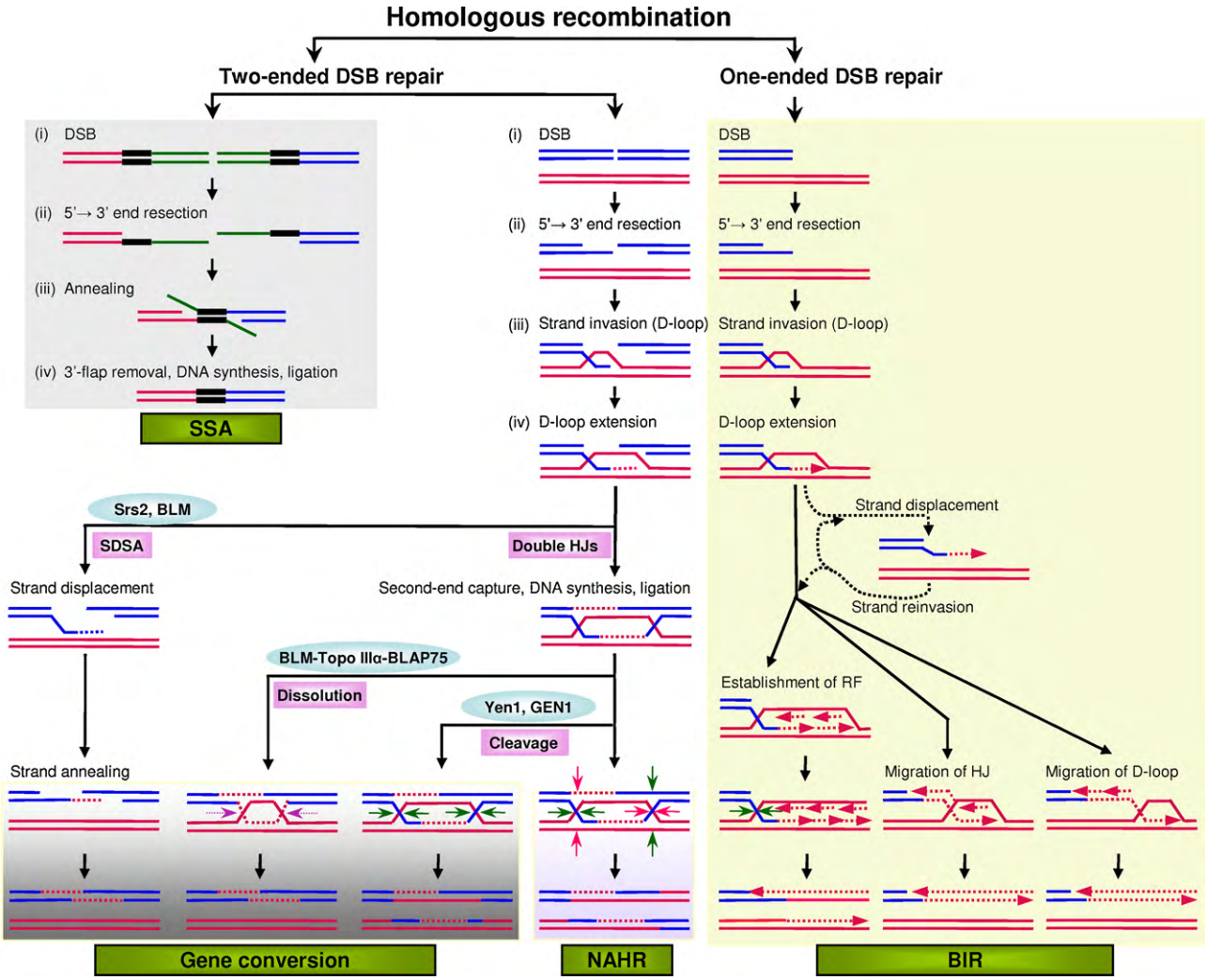

Fig. 1. Mutational models of homologous recombination. In the models of gene conversion, NAHR (non-allelic homologous recombination) and BIR (break-induced replication), the invading strand invariably binds to a homologous sequence. In the model of SSA (single-strand annealing), the black bars indicate the direct repeats that flank a DSB (double-strand break). In the dissolution model of gene conversion, the two facing horizontal purple arrows indicate convergent branch migration. In the double HJs (Holliday junctions) cleavage model of gene conversion, the four horizontal green arrows indicate the orientation of resolution. In the double HJ cleavage model of NAHR, the double HJs can be cleaved as indicated by the green arrows or by the red arrows. In the first pathway of BIR, the HJ is resolved as indicated by the facing horizontal green arrows. See text for details. D-loop, displacement loop; RF, replication fork; SDSA, synthesis-dependent strand annealing.