DNA Repair xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

DNA Repair

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

Review

Mismatch repair and homeologous recombination

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ARTICLE INFO

Article history:
Received 13 October 2015
Received in revised form 26 October 2015
Accepted 30 November 2015
Available online xxx

Keywords:
Mismatch repair
Homologous recombination
Homeologous recombination
Antirecombination
Heteroduplex rejection

ABSTRACT

DNA mismatch repair influences the outcome of recombination events between diverging DNA sequences. Here we discuss how mismatch repair proteins are active in different homologous recombination subpathways and specific reaction steps, resulting in differential modulation of these recombination events, with a focus on the mechanism of heteroduplex rejection during the inhibition of recombination between slightly diverged (homeologous) DNA sequences.

Contents

1. Introduction

DNA mismatch repair (MMR) increases the fidelity of replication by detecting and replacing misincorporated nucleotides [1–3]. In addition, MMR is involved in mitotic and meiotic genetic recombination through repairing mismatches in heteroduplex regions, removing non-homologous tails, aborting homeologous recombination via heteroduplex rejection, and promoting recombination and cross overs during meiosis. The involvement of MMR in meiotic recombination is reviewed by Manhart and Alani in this issue [4]. Here we will consider the roles of MMR during somatic recombination processes.

Abbreviations: MMR, DNA mismatch repair; HR, homologous recombination; DSB, double strand break; ssDNA, single strand DNA; dsDNA, double strand DNA; SDSA, synthesis dependent strand annealing; DSBR, double strand break repair; CO, cross over; NCO, non cross over; SSA, single strand annealing; BIR, break induced replication.

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http://dx.doi.org/10.1016/j.dnarep.2015.11.010
1568-7864/

2. DNA mismatch repair in the correction of replication errors

Canonical DNA MMR is replication-coupled and consists of four major phases, (i) detection of the mispaired base, (ii) identification of the nascent strand containing the incorrectly incorporated nucleotide, (iii) endo- and exonucleolytic removal or displacement of the nascent strand and (iv) resynthesis and ligation to restore the correct DNA sequence [1]. The mechanism and details of this pathway are extensively reviewed in other contributions of this issue, and here we only mention aspects directly relevant for the role of MMR in controlling recombination. These aspects are the following; (1) mismatches are detected by homodimeric (or homotetrameric) MutS in prokaryotes, and in eukaryotes by heterodimeric MutSα (MSH2/MSH6) and MutSβ (MSH2/MSH3) (Fig. 1 in [5]). (2) Mismatch detection triggers ATP-dependent sliding clamp conformations in these proteins which results in mismatch release and diffusion along the DNA helix (Fig. 4 in [6]). (3) This allows complex formation with homodimeric MutL (in prokaryotes) or heterodimeric MutL homologs (mainly MutLα, consisting of MLH1/PMS2 in humans and Mlh1/Pms1 in yeast) [7], (Fig. 1 in [8]). (4) These complexes initiate strand discrimination through endonuclease activation (MutH or the endonuclease activity within MLH1) [7–9]. (5) After incision of the nascent DNA strand, prokaryotic MutL recruits UvrD helicase to unwind the DNA from the strand incision towards the mismatch [7] (Fig. 1 in [8]). (6) Eukaryotic strand excision does not depend on helicase activity but relies on either ExonucleaseI (EXOI) or the strand displacement activity of the replicative polymerase to remove the strand containing the incorrect nucleotide [9].

3. Homologous recombination

Homologous recombination (HR) is involved in the repair of DNA double strand breaks (DSBs) and the rescue of stalled or collapsed replication forks, and is highly conserved throughout evolution [10]. The strand exchange proteins (i.e. RecA and its homologs) that mediate the core events of homology search, strand exchange and heteroduplex extension are found in a wide variety of organisms including bacteriophages, bacteria, archaea and eukaryotes [11–13]. HR is predominantly an error-free pathway, because it uses additional copies of homologous DNA sequences as repair template [14]. Repair of DSBs starts with processing of the ends of the broken DNA molecules into overhangs with 3'-terminated ends (Fig. 1A). This processing is carried out in a highly coordinated manner by multiprotein complexes combining helicase and nuclease activities with the ability to load the RecA or RAD51 strand exchange proteins onto the processed single-stranded (ss) DNA (reviewed in [15,16]).

During this initial stage (pre-synapsis), RecA/Rad51 monomers polymerize onto ssDNA to form a helical nucleoprotein filament that is active in homology search. Synapsis is the subsequent stage when non-homologous and homologous contacts are made during the search for homology. Upon homologous pairing between a segment of RecA-ssDNA filament and dsDNA, strand exchange takes place and a joint molecule is formed, also referred to as a D-loop (Fig. 1B). This D-loop structure is a precursor for multiple HR subpathways (see below). The dynamics of its formation and dissociation are highly regulated by mediator proteins [16,17]. Nascent D-loops are either extended to feed into one of the HR subpathways, or disassembled and thus aborting the HR reaction. Extended D-loops are disassembled during synthesis-dependent strand annealing (SDSA) (see below) as an anti-crossover mechanism. In this way D-loop stability is a major factor in determining HR subpathway choice and recombination outcome.

In the double-strand break repair (DSBR) subpathway (Fig. 1C), branch migration in the D-loop structure results in DNA heteroduplex extension, which allows capture of the second end of the broken DNA. Upon DNA synthesis to fill in the gaps, a double Holliday junction is formed. These junctions are resolved by structure-specific nucleases, resulting in multiple cross over (CO) events during meiosis but mainly non-cross over (NCO) events during somatic growth. A major alternative pathway in somatic cells is the SDSA pathway (Fig. 1D), in which second-end capture does not occur but the heteroduplex region is disassembled after extension of the first D-loop. This allows strand annealing of the ssDNA end of the break to the other end without formation of an additional D-loop, followed by DNA synthesis. SDSA solely results in NCO events. Alternatively, when the second end is not used or not available, repair can occur via the break-induced replication (BIR) pathway in which extensive parts of one DNA molecule are copied to restore a second copy (Fig. 1E).

In addition to these HR subpathways, an alternative route is available if repetitive sequences are present in the end-processed regions of the DSB. In this case, instead of being bound by the RecA/RAD51 strand exchange proteins, the ssDNA may anneal directly (in a Rad52-dependent manner), and after further processing of overhanging ends and DNA synthesis to fill in the gaps, a double-stranded (ds) DNA molecule is restored which contains deletions when compared to the original molecule. This single strand annealing process (SSA; Fig. 1F) is thus an error-prone, RecA/RAD51-independent subpathway [16].

3.1. The involvement of MMR proteins in HR processes

Recombining DNA sequences of homologous chromosomes are not always identical. Furthermore, recombination may occur between repetitive DNA in eukaryotic genomes, potentially causing deleterious chromosomal rearrangements [18]. In prokaryotes, processes such as conjugation may involve transfer of non-identical DNA sequences. Recombination between DNA partners that are not 100% identical generates mismatches within the heteroduplex region of the strand-exchange products. These mismatches act as substrates for the activation of the MMR pathway. Depending on which HR subpathway is operative, the number of mismatches encountered, or the specific reaction step at which this recognition is taking place, the outcome of MMR activity on the HR event may differ.

One possible outcome is that mismatches formed in the heteroduplex region will activate MMR proteins to initiate a complete repair reaction. Depending on which strand within the heteroduplex is targeted by MMR proteins, this will result in gene conversion or simply restoration [19,20] (circular arrows in Fig. 1). This could occur either during initial strand exchange or after the formation of CO and NCO recombination products, but is generally believed to occur during late steps of the recombination reaction when *de novo* DNA synthesis has been initiated. The mechanism of these repair reactions is believed to be identical to canonical MMR (except for its coupling to the replication machinery during S-phase), with excision and repair usually being targeted to the invading strand resulting in gene conversion. If mismatches fail to be detected or repaired, for example in MMR-deficient cells, gene conversion is reduced. In meiotic cells, postmeiotic segregation (PMS) events are concomittantly increased (observed in yeast as aberrant 5:3 segregation of spores rather than 6:2, indicative of gene conversion, or 4:4 segregation) [19].

Alternatively, the detection of mismatches in heteroduplex regions by MMR proteins results in the inhibition of the recombination event between these divergent DNA sequences. This inhibition occurs during the early steps of recombination upon mismatch detection in the joint molecule, and involves the dismantling of

Please cite this article in press as: K.-C. Tham, et al., Mismatch repair and homeologous recombination, DNA Repair (2015), http://dx.doi.org/10.1016/j.dnarep.2015.11.010