Published in final edited form as:

Crit Rev Biochem Mol Biol. 2012 May ; 47(3): 297–313. doi:10.3109/10409238.2012.675644.

Multiple cellular mechanisms prevent chromosomal rearrangements involving repetitive DNA

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Abstract

Repetitive DNA is present in the eukaryotic genome in the form of segmental duplications, tandem and interspersed repeats, and satellites. Repetitive sequences can be beneficial by serving specific cellular functions (e.g. centromeric and telomeric DNA) and by providing a rapid means for adaptive evolution. However, such elements are also substrates for deleterious chromosomal rearrangements that affect fitness and promote human disease. Recent studies analyzing the role of nuclear organization in DNA repair and factors that suppress non-allelic homologous recombination have provided insights into how genome stability is maintained in eukaryotes. In this review we outline the types of repetitive sequences seen in eukaryotic genomes and how recombination mechanisms are regulated at the DNA sequence, cell organization, chromatin structure, and cell cycle control levels to prevent chromosomal rearrangements involving these sequences.

Keywords

repetitive DNA; genome stability; genetic recombination; DNA repair; nuclear organization

Introduction

Repetitive DNA is present throughout the eukaryotic genome; for example, centromeres and telomeres are composed of repeated elements, ribosomal DNA consists of tandem arrays, and different classes of transposable elements are present in multiple copies. Repetitive DNA provides a means for co-evolving multiple forms of a gene and for rapidly reorganizing the genome (Marques-Bonet and Eichler, 2009; Ohno et al., 1968). The amounts and types of repetitive DNA varies between organisms and may reflect how rapidly an organism evolves to changes in its environment. Such benefits, however, come with risks. For example, repetitive DNAs serve as substrates for chromosomal rearrangements that include disease-causing deletions, inversions, and translocations (collectively defined as gross chromosomal rearrangements, GCRs; reviewed in Chen J-M et al., 2010).

The consequences of GCRs will depend largely on when and where they occur. An aberrant recombination event has a greater likelihood of contributing to disease if it occurs during meiosis or in the germ-line of a multicellular organism, rather than in a somatic cell. GCRs

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Declaration of interest

E. A. was supported by Award Number R01GM053085 from the National Institute of General Medical Sciences. C. M. G. was funded by an NIH training grant awarded to Cornell University. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of General Medical Sciences or the National Institutes of Health.

in the germ-line, if they do not confer lethality during meiosis or embryogenesis, will be passed on to all cells of the body. Thus a genetic disease can result if the GCR greatly affects the normal function of any organ or tissue. If the same rearrangement occurs in a single somatic cell of a multicellular organism, that cell will most likely be eliminated and not affect the rest of the organism. An exception is if a somatic GCR affects a tumor suppressor gene or a cell cycle control pathway and allows uncontrolled cell proliferation of the affected cell, leading to the growth of a potentially cancerous tumor.

Both germline and somatic GCRs are frequently seen in human cancers, and as many as hundreds to thousands of GCRs can exist within a single tumor (Chen J-M et al., 2010; Stratton et al., 2009; Velculescu, 2008). In some cases, recurrent GCRs are found in tumor suppressors or oncogenes. Two well-known GCRs are chromosomal translocations that create *BCR-ABL* fusions seen in chronic myeloid leukemias (Chen et al., 2010) and the intrachromosomal rearrangements within the *BRCA1* and *BRCA2* genes that are found in some breast and ovarian cancers (Sluiter and van Rensburg, 2011). Also, many inherited neurological, muscular, and blood disorders are caused by germ-line rearrangements between sequences present in non-allelic chromosomal positions (Stankiewicz and Lupski, 2002), and smaller scale rearrangements, such as trinucleotide repeat (TNR) expansions and contractions, appear to be the primary cause of neurodegenerative diseases including Parkinsons, Huntingtons and Fragile X Syndrome (Kovtun and McMurray, 2008).

In this review we will briefly introduce the common types of repetitive elements that are present in eukaryotic cells. We will then describe the most common rearrangement events involving these sequences. Finally we will describe recent studies, that describe regulatory mechanisms that prevent such events from occurring, and outline the benefits and consequences of chromosomal rearrangements for uni- vs. multi-cellular organisms.

Types of repetitive DNA and why they exist

A. Segmental duplications

Segmental duplications (Figure 1A), also referred to as low-copy repeats, are among the most deleterious of repetitive sequences because rearrangements in some of these sequences are associated with disease and occur more frequently than predicted (Shaw and Lupski, 2004; Lupski and Stankiewicz, 2005). Segmental duplications, which can involve chromosomal regions of one to several hundred kilobases (KB), have arisen recently during evolution, most likely as the result of unequal sister chromatid recombination between smaller repetitive elements and replication errors (see below). They appear unique to higher order primates and compose 5 to 10% of their genomes (Marques-Bonet and Eichler, 2009; Stankiewicz and Lupski, 2006; Bailey et al., 2001). However, some lower order organisms show evidence of whole or partial genome duplications which may have served a similar evolutionary role as segmental duplications (Timusk et al., 2011; Wolfe and Shields, 1997; Zhang et al., 2010; Zhou et al., 2011; Gu et al., 2004). The short time for divergence of the duplicated sequences has resulted in large genomic regions that share high (88 to 99%) sequence identity. The duplicated sequences arranged adjacently or on separate chromosomes can contain single or multiple genes. Segmental duplications are thought to contribute to evolution by providing the means for multiple copies of important genes to diverge and give rise to paralogs with specialized functions that can act in different environments and/or cell types (e.g. Ohno et al., 1968; Gu et al., 2004).

Segmental duplications pose threats to genome stability because they can serve as substrates for non-allelic homologous recombination (NAHR) using repair mechanisms that the cell normally uses to maintain genome stability (Shaw and Lupski, 2004; Figure 1B; Figure 2). Crossing over and non-conservative recombination events between segmental duplications

can result in GCRs such as deletions, duplications, inversions, and translocations, which can in turn subject the cells to gene dosage effects, perturbations in chromosome structure, and defects in chromosome segregation (Stankiewicz and Lupski, 2006). Similar types of rearrangements occur with significant frequency between gene paralogs and ectopic sequences in budding yeast (Jinks-Robertson and Petes, 1985, 1986; Lichten et al., 1987; Bailis et al., 1992; Putnam et al., 2009; Kolodner et al., 2002), making this organism a model for studying instability of segmental duplications.

B. Tandem and interspersed repeats

Tandem repeats (Figure 1A) are multiple iterations of a few hundred to a few thousand base pairs that are often arranged in arrays of a few or many repeats. These repeats can also be interspersed throughout the genome, and can be arranged in direct or inverted orientations. However, inverted repeats are extremely unstable because they can form secondary structures that disrupt DNA replication, and consequently, are rarely seen (Cook et al., 2011; Kurahashi et al., 2009; Paek et al., 2009; Lobachev et al., 2002). Many tandem and interspersed repeats are active transposons such as Ty elements in yeast, or have their origins in transposable elements, the most common of which are *Alu* and *LINE* elements in humans. Approximately 50% of the human genome is derived from transposable elements (International Human Genome Sequencing Consortium, 2001). In addition, ribosomal DNA exists in highly repetitive arrays that are condensed into highly packed chromatin (Németh and Längst, 2011).

Like segmental duplications, tandem and interspersed repeats are substrates for NAHR (Jeffreys et al., 2004; McVean, 2010). Packing of ribosomal DNA and some high copy sequences, such as Ty elements in yeast, into compact heterochromatin-like structures prevents the formation of DNA lesions (e.g. DSBs) that initiate recombination, thus providing a mechanism to prevent recombination between these sequences (Ben-Aroya et al., 2004). However, sequences such as *Alu* and *LINE* elements are frequently found at the breakpoints of disease-associated rearrangements, suggesting that they act as recombination hotspots, perhaps by forming structures that disrupt DNA replication (Argueso et al., 2008; Narayanan et al., 2006; Puget et al., 2002; Lobachev et al., 2002; Abeysinghe et al., 2003; Pentao et al., 1992; reviewed in Chan and Kolodner, 2011). Consistent with this idea, some repetitive arrays are thought to form DNA structures that are more sensitive to breakage during DNA replication (Chuzhanova et al., 2009; Lobachev et al., 2002; Figure 3), whereas others carry signature hotspot sequences that are known to increase their sensitivity to recombination by up to 10-fold (McVean, 2010; Myers et al., 2005, 2006, 2008). For example, the *RFB* and *HOTI* sequences increase recombination frequency within the ribosomal DNA array in budding yeast (Ward et al., 2000). Interestingly, recombination between *Alu* elements in the germ line appears to be a major route for generating segmental duplications (Shaw and Lupski, 2004; Zhou and Mishra, 2005; Bailey et al., 2003). Why do cells maintain repetitive sites that are hotspots for recombination? One possibility is that such events contribute to the adaptation of a species in specific environments by altering genome organization while specifically avoiding recombination within essential genes (McVean, 2010).

C. Satellites

Satellite sequences are also tandem repeats but differ from larger tandem repeats in their overall size (1 to ~ 100 nt), function, location and mode of instability (Figure 1A). Satellites are subdivided into minisatellites (14–100 nt) and simple sequence repeats, or microsatellites (1 to 13 nt), which tend to occur within non-coding DNA but may also occur in coding regions (Richard and Pâques, 2000). Simple sequence repeats constitute roughly 3% of the human genome (International Human Genome Sequencing Consortium, 2001).

Essential genomic features such as centromeres and telomeres are composed of satellite sequences that could thus protect them from the loss of unique functional sequences. Some satellite sequences are highly unstable, undergoing frequent expansions and contractions when reaching a threshold repeat size. Though satellites could undergo homologous recombination in the presence of double-strand breaks, their instability is thought to result primarily from strand slippage during replication (Richard and Pâques, 2000; Cleary and Pearson, 2005; Strand et al., 1993; Figure 3). Extensive expansions of satellite sequences, especially trinucleotide repeats, have been associated with neurological diseases and cancer (Claij and te Riele, 1999; Hannan, 2010). Literature regarding the dynamics of simple sequence repeats is vast; see Kovtun and McMurray (2008) for an excellent review of the evolutionary significance, mechanisms, and diseases associated with trinucleotide repeat expansion.

Mechanisms of recombination between repetitive elements

Homologous recombination (Figure 2) is a major cellular mechanism for repairing DNA lesions that appear due to DNA replication errors (Paques and Haber, 1999; Krogh and Symington, 2004). Homologous recombination also repairs DNA lesions resulting from environmental insults that occur during and outside of DNA replication. A single-stranded DNA gap or a stalled replication fork can induce homologous recombination, primarily through processing steps that create double-strand breaks (DSBs; e.g. Lobachev et al., 2002; Figure 3). Much of what is known about DSB repair pathways in eukaryotes has been obtained from work in the budding yeast *Saccharomyces cerevisiae*. Almost all of the repair factors identified in yeast have homologs in other eukaryotes, suggesting that DSB repair mechanisms are functionally conserved (reviewed in Paques and Haber, 1999; Krogh and Symington, 2004).

Homologous recombination is regulated by the type of initiating lesion and the time at which it occurs in the cell cycle. For example, during meiosis in budding yeast, repair of programmed DSBs is biased towards an allelic template located on a homologous chromosome (Roeder, 1997). The distribution of DSBs and repair bias results in the formation of crossovers between all homologs and is critical for the proper alignment and segregation of homologous chromosomes in Meiosis I. In somatic growth, repair events that lead to crossing over between homologs are rare; other types of recombination are promoted such as double-strand break repair (DSBR) involving sister chromatids, synthesis-dependent strand annealing (SDSA), break-induced recombination (BIR) and single-strand annealing (SSA; Krogh and Symington, 2004; Paques and Haber, 1999; see below). By restricting repair between repetitive DNA sequences in non-allelic positions during somatic growth, the cell can avoid crossover events that can lead to chromosomal translocations, inversions and deletions. Below we will briefly summarize DSB repair pathways using the budding yeast nomenclature. We will indicate differences in nomenclature for the higher eukaryotic organisms when appropriate. Extensive reviews have been written on homologous recombination mechanisms (Pâques and Haber, 1999; Krogh and Symington, 2004; Mimitou and Symington, 2009a; Mimitou and Symington, 2009b; Mimitou and Symington, 2011; Symington, 2002); we will briefly discuss the currently accepted models for homologous recombination as they pertain to events involving repetitive DNA sequences.

A. DNA repair that can lead to crossing over: the canonical DSBR pathway and BIR

DSBs created by nucleases in somatic growth and meiosis are primarily shuttled into a DSBR pathway in which the 5' strands on each end of the DSB are subject to nucleolytic degradation, revealing 3' ended single-stranded DNA (ssDNA; Szostak et al., 1983; Figure 2A). This 5' to 3' resection is initiated by Mre11-Rad50-Xrs2 (MRX; MRN in mammals) and Sae2 and will utilize either Exo1 or Sgs1-Top3-Rmi1 (BLM-TopoIII-RMI1 in

mammals) and Dna2 for further resection (Tsubouchi and Ogawa, 2000; Gravel et al., 2008; Mimitou and Symington, 2008; Zhu et al., 2008; Mimitou and Symington, 2009a). The naked ssDNA is rapidly coated by the ssDNA binding protein RPA, which is thought to protect the ssDNA from forming secondary structures that inhibit repair. In a series of steps involving multiple factors, RPA is replaced by Rad51, resulting in a nucleoprotein complex capable of invading into a complementary double-stranded DNA (dsDNA) template (Sugiyama et al., 1997; Sung et al., 2003). When one of the ssDNA ends invades a homologous template it will form a stable strand invasion “D-loop” intermediate and serve as a primer for DNA synthesis. Rad52 assists Rad51 filament formation by directly interacting with RPA and making it amenable to displacement by Rad51 (Sung, 1997; Sugiyama and Kowalczykowski, 2002). In addition, it promotes strand invasion by stabilizing the displaced ssDNA of the D-loop. Rad52 is also thought to assist the displaced DNA within the D-loop to capture the second ssDNA end and initiate strand synthesis, leading to the formation of a double-Holliday junction (dHJ) structure (Nimonkar and Kowalczykowski, 2009; Lao et al., 2008).

Double Holliday junctions can undergo branch migration to extend the region of sequence that will be involved in the recombination event. Less is known about the factors that promote branch migration in eukaryotes, but it appears that Rad54 and the Mph1 and Sgs1 helicases can modulate branch migration (Bugreev et al., 2006; Lo et al., 2006; Rossi and Mazin, 2008; Tripathi et al., 2007; Zheng et al., 2011). Finally, the dHJ is resolved by one of three mechanisms: 1. Resolution by an endonuclease (e.g. Mus81-Mms4 or Yen1/human GEN1) to create either a crossover or non-crossover product; 2. Dissolution by a helicase-topoisomerase (Sgs1-Top3-Rmi1/human BLM-TopoIII-RMI1) to create a non-crossover; 3. Removal of the dHJ during normal replication (Svendsen and Harper, 2010; Ira et al., 2003; Ashton et al., 2011; Plank et al., 2006; Hickson and Mankouri, 2011; Dayani et al., 2011; Esposito, 1978).

It should be noted that dHJs are thought to be resolved by endonucleases during meiosis to promote crossover formation, whereas recombination intermediates involving homologs in somatic growth are thought to be dissolved by Sgs1-Top3-Rmi1 to promote intersister or intrachromosomal recombination (Dayani et al., 2011; Matos et al., 2011).

In contrast to recombination that occurs in meiosis, random DSBs that appear during vegetative (or somatic) growth primarily use the sister chromatid as a template for repair (Kadyk and Hartwell, 1992; reviewed in Krogh and Symington, 2004). Such a repair bias is thought to prevent interactions between chromosomes (both homologous and non-homologous) that could increase the likelihood of a chromosomal rearrangement. The resulting sister chromatid repair will not result in mutations unless mistakes are made during repair or repair occurs through unequal sister chromatid exchange (Petes, 1980; Szostak and Wu, 1980). In cases where a sister chromatid is unavailable, for example, a haploid yeast cell in G1 phase, a DSB is most often repaired non-conservatively by the non-homologous end joining pathway (NHEJ; reviewed in Symington and Gautier, 2011).

A specialized type of DSB, BIR (Figure 2B), has been described which appears important for rescuing degraded chromosome arms and for maintenance of telomeres (reviewed in Kraus et al., 2001), and can be viewed as creating non-reciprocal or “half” crossover products. In BIR, a resected DNA end has formed a D-loop with a homologous template and begins replication. However, when it is unable to identify the second broken end, either because it is trapped in another repair intermediate or has been degraded, the first end will continue to replicate (McEachern and Haber, 2006; Llorente et al., 2008). Replication will continue until the second break end is found or replication reaches the end of the chromosome. Consequently BIR can result in extensive gene conversion tracts (up to a few

hundred KB) or copying of an entire chromosome arm that may or may not be from a homologous chromosome.

B. DSB repair that does not involve crossing over: SDSA and SSA

When a sister chromatid is available, in S or G2 phase for example, crossing over is suppressed and most of the breaks are shuttled into the SDSA pathway (Ira et al., 2003; Figure 2C). The resection step of SDSA is essentially the same as for DSB repair. Like DSB repair, one or both of the break ends will proceed to create a D-loop with a homologous chromosome, but instead of assembling both ends into a dHJ structure, the D-loop(s) will dissociate and the newly copied DNA ends will anneal to each other. At this point, further DNA synthesis can occur to fill in any gaps and DNA ligase is required to seal the nicks. Only non-crossover products are formed by SDSA.

SSA (Figure 2D) allows rapid repair of breaks within tandem repeat arrays, for example at the yeast and mammalian ribosomal DNA loci (Liang et al., 1998; Elliott et al., 2005; Fishman-Lobell et al., 1992; Liefshitz et al., 1995; Park et al., 1999). SSA initiates at resected DSB ends, but unlike other types of homologous recombination, it is intrachromosomal; it does not involve strand invasion and does not require a homologous chromosome or sister chromatid. Consistent with this, SSA can occur independently of Rad51 but is dependent on strand annealing factors such as Rad52 and Rad59 (Fishman-Lobell et al., 1992; Davis and Symington, 2001). In fact, Rad51 must be excluded so that Rad52 can instead catalyze strand annealing of the two complementary repetitive elements that have been revealed on opposite ssDNA ends (Wu et al., 2008; Sugiyama and Kantake, 2009). After annealing, intervening non-homologous DNA is displaced as 3' ssDNA tails and are clipped off by the Rad1-Rad10 endonuclease. DNA synthesis fills the gaps and DNA ligase seals the nicks. Since SSA results in deletions it is not conservative. However, the deletions are typically small; SSA does not occur between repeats spaced much more than 5 kb apart (Jain et al., 2009), and they may offset repeat expansions that occur frequently during replication (Kobayashi, 2011).

Suppression of NAHR

All of the homologous recombination pathways described above require a template to repair the DNA lesion; in diploids there are at most three templates located in allelic chromosomal positions; one on the sister chromatid and two on the homolog. What would happen if a resected DNA end first found a template in a non-homologous chromosome? Studies performed in budding yeast grown vegetatively or induced to enter meiosis have shown that gene conversion and crossing over between ectopic or dispersed homologous sequences can occur frequently (Jinks-Robertson and Petes, 1985, 1986; Lichten et al., 1987; Bailis, 1992). A screen in budding yeast (Putnam et al., 2009), using substrates that resemble segmental duplications in mammalian cells, showed that homologous recombination, DNA mismatch repair, and DNA damage checkpoint pathways played specific roles in suppressing chromosomal rearrangements between the segmental duplication substrate compared to rearrangements involving single copy sequences. The above studies have encouraged us to entertain the following: 1. How does the DSB repair machinery direct broken ends to the "correct" template? 2. How does it decide how much homology is sufficient to ensure that the template chosen is an allelic sequence? 3. Is the homology decision process the same across species or cell types, or even at different times during cell growth and division? As outlined below, the relatively high stability of eukaryotic genomes is accomplished by regulating early (A) and subsequent (B) steps in homologous recombination and by cell cycle control (C) and cellular organization (D) mechanisms. The combination of these regulatory mechanisms results in the avoidance of recombination between closely related

non-allelic sequences yet permits recombination between slightly divergent allelic sequences.

A. Regulation of NAHR during the strand exchange step and strand annealing steps

As described above and in Figure 1, segmental duplications threaten genome stability because they can serve as substrates for NAHR. The initial strand invasion step (seen in DSBR, BIR and SDSA) in homologous recombination is sensitive to sequence heterology between the invading sequence and the template (reviewed in Surtees et al., 2004). For example, in baker's yeast, Rad51 is sufficient in promoting recombination between sequences with up to 10% sequence divergence (Datta et al., 1997). Using *in vitro* strand transfer reactions with the *S. cerevisiae* proteins, Holmes et al. (2001) demonstrated that Rad51-ssDNA is very efficient in promoting strand transfer between 3 KB substrates having a region of heterology up to 9-bp long, but was extremely inefficient in allowing transfer between substrates with 10 or more base pairs of heterology, indicating that there is a critical threshold for the amount of heterology that is tolerated during strand invasion. Similarly, Rad51 will allow branch migration across regions of heterology only up to 6 bp in length (Namsaraev and Berg, 2000). These studies, however, were limited by the use of insertion/deletion loop substrates, and the stringency of strand exchange was not tested with substrates containing single or multiple dispersed mismatched bases. For human Rad51, Gupta et al. (1999) demonstrated that as few as two mismatched bases within an 83-mer was enough to significantly impair strand exchange *in vitro* while 6 or 7 evenly spaced mismatches completely abolished strand exchange.

It is important to note that the activities of yeast and human Rad51 may be similar because both organisms share a similar minimal efficient processing segment (MEPS), which is defined as the smallest stretch of perfect homology that is needed for efficient recombination *in vivo*. This value is estimated to be approximately 200 bp for both mammals and yeast but only 23 to 90 bp for *E. coli* (Shen and Huang, 1986; reviewed in Waldman, 2008). The MEPS value, however, is likely to depend on factors in addition to Rad51; for example DNA mismatch repair proteins that act in heteroduplex rejection (see below) are likely to contribute.

Holthausen et al. (2010) suggested that the length of a continuous Rad51-ssDNA filament affects the ability of the strand exchange protein to bypass DNA sequence heterology, and may correlate with amount of repetitive sequence present in the host genome. Rad51 filament nucleation *in vitro* is less efficient than the bacterial strand exchange protein RecA and consequently Rad51-ssDNA filaments are less continuous and more flexible compared to RecA-ssDNA filaments. While having more flexibility may increase the rate of homology search (allowing multiple contacts with dsDNA at once), the shorter stretches of Rad51-ssDNA filament may be incapable of stabilizing strand invasion intermediates with large regions of heterology. This could afford yeast and mammals a better chance at finding the proper homologous template within the densely packed structure of eukaryotic chromosomes while also giving them enough stringency to avoid NAHR within their highly repetitive genomes.

On the other hand, the structure of the filaments *in vivo* may not share the same amount of flexibility as suggested by *in vitro* nucleation reactions. The incorporation of Rad51 paralogs Rad55 and Rad57 into filaments (Liu et al., 2011) may alter their flexibility and bypass requirements (Ragone et al., 2008; Holthausen et al., 2010). Regardless, Rad51 and RecA require ATP hydrolysis for bypassing heterology, which in itself serves as a barrier to strand exchange between sequences of imperfect homology (Rosselli and Stasiak, 1991; Sung, 1994).

The mechanism by which the Rad51-ssDNA filament searches for homology and invades dsDNA is currently being investigated *in vitro* using single-molecule magnetic tweezer and total internal reflection fluorescence microscopy technologies. Studies using human Rad51 and *E. coli* RecA have been able to follow filament formation and strand invasion, respectively, in real time (Miné et al., 2007; van der Heijden et al., 2008). Single molecule studies with a variety of heterologous substrates should prove to be revealing about how and to what extent Rad51 and related proteins bypass heterology.

The strand annealing activity of Rad52 is also capable of bypassing limited amounts of heterology. For example, mismatch recognition and helicase mutants in yeast will allow SSA between tandem repeats sharing only 97% homology, indicating that Rad52 must allow efficient annealing between at least modestly divergent sequences (Sugawara et al., 2004). *In vitro* single-strand annealing by human Rad52 observed by fluorescence resonance energy transfer generated a model for the initial homology search and subsequent extension of annealing (Rothenberg et al., 2008). Initial homology is first identified in patches of four nucleotides followed by sampling of several adjacent nucleotides for homology. In order for annealing to initiate, there must be sufficient homology between the adjacent nucleotides such that annealing is more energetically favorable than the hRad52-ssDNA interaction, since hRad52 cannot be bound to dsDNA. The model predicts that a stretch of approximately ten complementary bases are required to initiate annealing. Extension of the annealed region is then predicted to occur in segments of several nucleotides. The segments are initially brought into proximity by the interaction of two hRad52 oligomers, one bound to each ssDNA, and if the ssDNA segments are sufficiently homologous they will anneal and release the hRad52 oligomers. Considering this mechanism, hRad52 may allow annealing across occasional single nucleotide mismatches that do not significantly contribute to the energetic transaction required for annealing, but more extensive regions of heterology would not be able to overcome the energy barrier unless they could be “looped out.” RPA could assist in annealing by removing secondary structure to open up the DNA for assembly of Rad52 oligomers and more efficient searching, and it may also minimize “loop out” structures that could be bypassed by Rad52. Indeed, appropriate concentrations of RPA can enhance hRad52-mediated annealing (Grimme et al., 2010). Continued single molecule studies with more diverse DNA substrates will reveal more specifically the extent to which Rad52 can bypass heterology.

Another possible level of regulation is control of homologous recombination through the Rad54 motor protein. Rad54 has been called the “Swiss Army knife” of HR (Heyer et al., 2006) because of its multi-functional roles at almost every step of homologous recombination. Rad54 is involved in stimulating strand invasion and D-loop formation through contacts with the Rad51 filament (Ceballos and Heyer, 2011; Kiianitsa et al., 2006), but perhaps more importantly, Rad54 is essential for the transition from strand invasion to recombination-associated DNA synthesis (Li and Heyer, 2009). In yeast, Rad54 is required to displace Rad51 from the 3'OH end of the invading strand to allow assembly of DNA polymerase δ for extension of the invading strand. But what inhibits Rad54 from displacing Rad51 prematurely or from a template of insufficiently homology? There is likely to be a minimum amount of homology, length, or level of stability of the D-loop that is required before DNA synthesis can be initiated. Research into the mechanism and homology requirements for this role of Rad54 is critical for determining whether it has a significant impact on NAHR. Furthermore, a role for mammalian Rad54 in initiating DNA synthesis from a D-loop has yet to be confirmed (Li and Heyer, 2009).

B. Regulation of NAHR: Disrupting heteroduplex intermediates (Figures 4 and 5)

Allelic sequences on homologous chromosomes can differ on the order of 1–2%; therefore regulation of NAHR must be finely balanced so that recombination with an extensively

divergent non-allelic sequence is avoided but recombination with an allelic sequence is allowed. Though strand annealing and exchange enzymes can limit NAHR between significantly divergent sequences (see above), they are not stringent enough to distinguish more closely related non-allelic sequences from minimally divergent allelic sequences. For this reason, organisms have evolved an additional level of regulation of NAHR that can disrupt heteroduplex recombination intermediates between modestly divergent sequences. These closely related sequences are often called homeologous sequences, and generally display sequence divergence of approximately 2–15%. Disruption of heteroduplex intermediates, termed heteroduplex rejection, involves the concerted action of mismatch repair (MMR) proteins, helicases, and topoisomerases (Sugawara et al., 2004; Surtees et al., 2004; Bailis et al., 1992; George and Alani, unpublished results).

DNA MMR proteins are commonly known for their role in repairing mismatched bases arising during replication. The MMR system in eukaryotes is composed of two mismatch recognition heterodimers: Msh2-Msh6 which identifies single-base mismatches and insertion/deletion loops of 1–2 bases and Msh2-Msh3 which recognizes larger insertion/deletion loops. An additional heterodimeric complex Mlh1-Pms1 transmits the MMR signal to nucleases including Exo1, which excise the nascently replicated strand containing the DNA mismatch (reviewed in Kolodner and Marsischky, 1999; Li, 2008). Extensive evidence for MMR proteins suppressing homeologous recombination has been obtained in bacteria and lower and higher eukaryotes (reviewed in Surtees et al., 2004). Studies in yeast using recombination reporter cassettes revealed that MMR mutants show increased crossing over and more extensive gene conversion tracts (Datta et al., 1997; Datta et al., 1996; Chen and Jinks-Robertson, 1998; Selva et al., 1995), suggesting that MMR factors act at both early and late stages of homologous recombination, perhaps to minimize both strand exchange and branch migration in the presence of heterology. Other work (e.g. Nicholson et al., 2000) showed that the substrate specificities of Msh2-Msh3 and Msh2-Msh6 for suppressing recombination in heteroduplex intermediates were similar to their specificities during mismatch recognition in MMR. Mlh1-Pms1 and Exo1 play relatively minor roles in suppressing recombination, suggesting that heteroduplex rejection may not require a strong need for transduction of a signal to downstream nucleases. Consistent with distinct functions for MMR and heteroduplex rejection, a recent study in which Msh2-Msh6 function was restricted to a specific stage in the cell cycle indicated a coupling of MMR but not heteroduplex rejection to DNA replication (Hombauer et al., 2011).

It is now accepted that MMR factors, RecQ helicases (Sgs1), and type III topoisomerases (Top3-Rmi1) are primarily responsible for disrupting heteroduplex intermediates, but how their activities are coordinated on various types of recombination intermediates is still under active investigation (Nicholson et al., 2000; Sugawara et al., 2004; Goldfarb and Alani, 2005; Mankouri et al., 2011; Lo et al., 2006; Watt et al., 1996; Raynard et al., 2006; Ira et al., 2003). Furthermore, there are multiple steps where heteroduplex rejection might occur such as during strand invasion, extension of the invading strand, annealing of newly replicated strands (SDSA), second-end capture, and branch migration (DSBR). To study heteroduplex rejection in a simplified system that could ultimately be studied *in vitro*, the Haber and Alani labs used an SSA-based assay (Sugawara et al., 2004; Goldfarb and Alani, 2005) in which there is only a single heteroduplex intermediate. This assay revealed that Msh2-Msh6 and Sgs1-Top3-Rmi1 were required to disrupt annealed heteroduplex intermediates between 3% divergent sequences by a conservative unwinding mechanism (Sugawara et al., 2004; Goldfarb and Alani, 2005; C. George and E. Alani, unpublished observations). Mlh1-Pms1, Exo1, and other helicases (e.g. Srs2) did not have a role in rejecting the heteroduplex intermediate, and Msh2-Msh3 could not be tested due to its requirement for 3' non-homologous tail removal during SSA.

The current model for heteroduplex rejection during SSA is that base mismatches and insertion/deletion loops within heteroduplex intermediates are recognized by the Msh proteins which directly interact with Sgs1 to stimulate unwinding of the heteroduplex DNA (Figure 4). Top3-Rmi1 may be required to relieve supercoils during unwinding, to stimulate Sgs1 helicase activity, or to direct it to the ssDNA tails on the SSA intermediate. Several observations support this model. First, both yeast Sgs1 and human RecQ helicases can physically interact with Msh6 (Doherty et al., 2005; Saydam et al., 2007; Yang et al., 2004; A. Lyndaker and E. Alani, unpublished results), and RecQ helicase activity is stimulated by human MSH6 (Yang et al., 2004). Furthermore, *in vitro* Sgs1 binds to and unwinds 3'-tailed substrates similar to the structure of SSA intermediates and is strongly stimulated in the presence of Top3-Rmi1 (Cejka and Kowalczykowski, 2010; Cejka et al., 2010; Bennett et al., 1998; Bennett et al., 1999).

The molecular switch model has become an important hypothesis to explain how mismatch recognition and downstream steps in MMR are coordinated (Acharya et al., 2003). This model is supported by experiments suggesting that mismatch binding by Msh protein triggers an ADP → ATP exchange that enables it to enter a sliding clamp diffusion mode (Kunkel and Erie, 2005; Jiricny, 2006). In one version of the model, mismatch recognition stimulates Msh complexes to move away from a mismatch site until it encounters a signal (e.g. a DNA nick or PCNA loaded at a nick). Based on such studies one can imagine that mismatch recognition during heteroduplex formation would stimulate Msh2-Msh6 to search for factors that modulate recombination. For example, during SSA, upon mismatch recognition Msh2-Msh6 may recruit Sgs1 to the 3' tail or encounter Sgs1 upon reaching the tail, after which the Sgs1 helicase is activated. In the event of larger or more complex heteroduplex intermediates (i.e. strand invasions or Holliday junctions, Figure 5), Msh2-Msh6 may be more likely to encounter nicks, gaps, or an active replication fork and will instead stimulate Mlh1-Pms1, which could either participate in repair of the mismatch or modulate disruption of the heteroduplex through an alternative (possibly nucleolytic) mechanism. Such a model would be consistent with the modest role of Mlh1-Pms1 and Exo1 in heteroduplex rejection during the inverted repeat assay (Nicholson et al., 2000) but not the direct repeat assay (Sugawara et al., 2004). Current studies in our laboratory are aimed at confirming and distinguishing between these proposed models using a chromatin immunoprecipitation approach and to explore the role (if any) for PCNA in heteroduplex rejection during SSA.

In addition to rejection mechanisms that involve MMR factors, several helicases have been shown to prevent crossover formation during DSB repair and could thus prevent NAHR. Yeast Mph1 and human RTEL1, for example, dissociate D-loops to promote non-crossover rather than crossover repair of a DSB (Prakash et al., 2009; Barber et al., 2008). Srs2 discourages homologous recombination by dismantling Rad51 pre-strand invasion filaments (Krejci et al., 2003; Veaute et al., 2003). Also, in addition to its role in disrupting heteroduplex recombination intermediates (see above), Sgs1-Top3-Rmi1 and mammalian homologs suppress crossovers by dissolving dHJs (Ira et al., 2003; Ashton et al., 2011; Plank et al., 2006).

C. Regulation of recombination by cell cycle control: Limiting recombination to times when allelic templates are nearby

The initiating event of homologous recombination is end resection. Resected ends are unstable (Zierhut and Diffley, 2008) and need to be engaged with recombination factors as soon as they are formed to ensure that they can easily find an appropriate complementary partner. Both yeast and mammals ensure that resection can only occur during the S and G2 stages of the cell cycle when allelic sequences in sister chromatids are in close proximity

(Aylon et al., 2004; Ira et al., 2004; Jazayeri et al., 2006; Huertas and Jackson, 2009; Symington and Gautier, 2011; reviewed in Lee and Myung, 2009).

Cyclin-dependent kinases (CDKs) that control progression through cell cycle stages also limit resection to the S and G2 stages. In budding yeast, the primary catalytic subunit of CDKs Cdk1, controls resection in at least two ways. First, resection is inhibited by the association of the Rad9 DNA damage checkpoint protein with broken DNA ends, blocking assembly of the resection machinery. This association of Rad9 with DSBs requires methylation of histone H3-K79 by the Dot1 methylase. Histone methylation generally results in chromatin compaction that in this situation suppresses DSB resection, rather than repressing transcription (El-Osta and Wolffe, 2000). Resection is initiated during S and G2 in a Cdk1-dependent manner, and Cdk1 dependency can be bypassed in a *rad9Δ* or *dot1Δ* mutant (Lazzaro et al., 2008). Presumably, a G2-phase expressed Cdk1-Clb modifies Rad9 to abolish the Rad9-histone interaction, releasing Rad9 from the DSB end and allowing resection. Alternatively, but perhaps not exclusively, a G1-expressed Cdk1-Cln may promote H3-K79 methylation and/or association of Rad9 with histone H3. The second level of control by Cdk1 is through direct modification of the resection machinery. Cdk1-Clb phosphorylates the Sae2 endonuclease which activates Sae2 activity in DNA end resection (Huertas et al., 2008). Regulation of resection through both Rad9 and Sae2 are functions conserved in the mammalian homologs 53BP1 and CtIP (Huertas and Jackson, 2009; Huyen et al., 2004).

During G0 or G1, resection is either absent or very limited. As a result, DSBs are typically repaired by non-homologous end joining (NHEJ; Zierhut and Diffley, 2008). Since DSBs may not be in proximity to allelic sequences during G0 and G1, NHEJ is preferable so that use of a non-allelic complementary sequence for homologous recombination is limited. As long as only one DSB is present, NHEJ will repair the break without GCRs. Though NHEJ is nonconservative, mutations would be limited to the region of the DSB and would pose less risk than would a chromosomal translocation. Spontaneous DSBs occurring during the mitotic cycle are rare (Lettier et al., 2006), so the likelihood of two or more DSBs occurring simultaneously and thus the potential for NHEJ-mediated translocation is extremely rare, provided the cell is not exposed to DNA-damaging conditions or is pre-disposed to chromosomal instability.

In addition to activation of resection during S and G2, recombination factors including Rad51 and Rad52 are expressed at higher levels during S and G2 in yeast (Chen et al., 1997), and proteins targeted to the nucleus by Cdk1 include Dna2 and the dHJ resolvase Yen1 (Chen et al., 2011; Kosugi et al., 2009). Both Mus81-Mms4 and Yen1 are also regulated in coordination with the cell cycle to limit crossover formation during mitosis (Matos et al., 2011). Clearly, regulation of homologous recombination is very intimately involved with cell cycle dynamics. It remains to be determined whether Cdk1 can control expression, activation, or nuclear localization of any other recombination factors or proteins that disrupt heteroduplex intermediates.

D. Regulation of recombination by chromosome organization: Restricting availability of potential non-allelic templates in space (Figure 6)

Chromosome pairing, also known as somatic pairing is a major form of regulation that restricts repetitive sequences in space (reviewed in Burgess et al., 1999). Work in budding yeast using fluorescence *in situ* hybridization analysis and recombination assays (Weiner and Kleckner, 1994; Burgess and Kleckner, 1999; Burgess et al., 1999) has shown that chromosome homologs are paired in vegetative growth but this pairing is disrupted in S-phase and in G2-arrested conditions. This pairing ensures that allelic DNA sequences are closer to each other relative to similar sequences located on nonhomologous chromosomes.

Burgess et al. (1999) suggest that “pairing may exist to promote juxtaposition of homologous regions within irregular genome complements.” Such pairing could thus serve to restrict the availability of potential non-allelic substrates.

In addition to pairing of allelic sequences, non-allelic sequences are sequestered from each other via organization of the nucleus. The nucleus of lower and higher eukaryotic cells is composed of distinct but dynamic sub-compartments that confine intranuclear processes to a limited space. (Léger-Silvestre et al., 1999). Recent chromosome conformation capture studies in yeast and human interphase cells have modeled these compartments in three-dimensional space. This work shows that highly repetitive, primarily non-coding, DNA is organized into heterochromatin domains located near the nuclear periphery. In mammalian cells, chromosomes are organized into their own stable globular territories, away from other chromosomes that may share similar sequences (Tanizawa and Noma, 2011; Duan et al., 2010; Figure 6A). Fractal-globule models (reviewed in Mirny, 2011) predict that globular territories are the natural folded state of individual chromosomes within the environment of the mammalian nucleus; however it is possible that a mechanism, perhaps analogous to chromosome motion mechanisms seen in meiosis in a variety of organisms, prevents individual chromosomes or domains from being tangled or interlocked during movement of chromosomes (Wanat et al., 2008).

The nucleolus, which has historically been a sub-compartment of mysterious function, is now being recognized as an extensively heterochromatic domain that houses and protects the repetitive ribosomal DNA arrays from genome instability (Chiolo et al., 2011). These observations are re-defining the term “heterochromatin;” rather than being defined by regions of gene silencing and characteristic marks such as methylated histones and the HP1 protein, they are being defined as regions of condensed repetitive DNA that are usually associated with these features (Peng and Karpen, 2008; Figure 6B). Heterochromatin is highly enriched for essential genomic features such as centromeres, telomeres, and ribosomal DNA, and is essential for their function and protection (Peng and Karpen, 2008). Heterochromatin is also enriched for satellites and transposable elements that are sequestered to prevent hyper-recombination (Slotkin and Martienssen, 2007). ‘

At first the idea of repetitive DNA being confined to a tightly packed region is counterintuitive to global chromosome pairing mechanisms that prevent the close alignment of non-allelic sequences that could participate in NAHR. However, such an organization provides the advantage of sequestering DNA packaged into heterochromatin from non-allelic sequences located in distant areas of the genome, leaving it at risk for only small-scale intrachromosomal instability. The take-home message from studies done so far is that repetitive DNA resides inside a heterochromatic environment where recombination using a homologous chromosome is suppressed and recombination that is intrachromosomal or with a sister chromatid is promoted.

Heterochromatin displays very limited γ H2AX foci (a DSB marker) compared to euchromatin following treatment with ionizing radiation (Costes et al., 2010); this observation suggests that heterochromatin is less accessible and possibly, less sensitive to DNA-damaging agents that initiate recombination. Such observations have led to the idea that genome stability of heterochromatin is maintained in a manner similar to heterochromatin-mediated gene silencing (Peng and Karpen, 2008; Osley and Shen, 2006).

Though chromatin dynamics involved in gene silencing have been extensively studied, chromatin dynamics in DSB repair is a very recent focus and is less clear. Like gene silencing, chromatin structure appears to regulate homologous recombination through two major mechanisms; histone modification and nucleosome remodeling (Peng and Karpen,

2008; Figure 7A). In yeast, modified histone components such as phospho-H2A and γ H2AX appear at sites of DSBs coincidentally with the chromatin remodelers SWI/SNF, RSC, and Ino80 (Shroff et al., 2004; Rogakou et al., 1999; Celeste et al., 2003; Shen et al., 2000; Chai et al., 2005). All three of these remodelers appear to be required for DSB repair in yeast (Chai et al., 2005; Shim et al., 2007; Morrison et al., 2004; van Attikum and Gasser, 2005; van Attikum et al., 2007; van Attikum et al., 2004), and similar roles for equivalent chromatin remodelers appear to be conserved in humans and *Drosophila* (Ogiwara et al., 2011; Park et al., 2010; Kusch et al., 2004). Histone modifications are thought to contribute to DSB-dependent chromatin remodeling by recruiting remodelers to the DSB (Ogiwara et al., 2011), and by modulating the localization of HR proteins to the break (Lazzaro et al., 2008; Osley and Shen, 2006; Oum et al., 2011; Tsukuda et al., 2009). In addition, RSC promotes loading of cohesins to the DSB site to hold sister chromatids close together, thereby restricting NAHR by promoting sister chromatid recombination (Figure 7A; Liang et al., 2007).

Chromatin remodeling surrounding DSBs within heterochromatin domains is critical for their repair by homologous recombination. Furthermore, if a DSB within a heterochromatic region has to be repaired using a homolog, it must be moved to a more euchromatic environment to do so. Recent work by Chiolo et al., (2011) in *Drosophila* showed that DSBs in heterochromatin could be resected quickly but had to be moved, by a yet to be understood mechanism, to the heterochromatin periphery and create a local environment more typical of euchromatin in order to have access to Rad51 for strand invasion (Figure 7B). Similarly, Torres-Rosell et al. (2007) showed that Rad52 was excluded from the nucleolus in yeast and had to be moved to an extranucleolar site for repair by HR. The reason for condensation of repetitive DNA into heterochromatin, then, may be to promote the use of non-conservative repair at times when homolog pairing is absent and non-allelic sequences are more available.

Closing thoughts

In this review, we outlined the numerous cellular and molecular mechanisms by which genome stability is maintained, particularly in the suppression of NAHR events that can create GCRs. GCRs are more destructive than other types of genomic alterations because they can disrupt multiple genes at once and alter chromosome organization, making cells more susceptible to DNA damage (Stankiewicz and Lupski, 2002). Furthermore, a chromosome that receives a large genomic alteration is often less stable, either due to altered chromatin status or as in the case of a dicentric chromosome, prone to further rearrangement (Schmidt et al., 2010; Hastings et al., 2009; Fournier et al., 2010). Multiple breakages and fusions of unstable chromosomes are thought to contribute to chromothripsis, the rapid bursts of large-scale genomic rearrangements that can be found in many cancerous tumors (Stephens et al., 2011).

Unicellular organisms such as budding yeast can better tolerate recombination during vegetative growth because, unlike multi-cellular organisms, a mutation that enhances the survival of a single cell can be passed to future generations and enhance survival of the species. Also a deleterious mutation in a uni-cellular organism will only eliminate a single cell (or small population of cells) without affecting survival of the species as a whole. In contrast, if a single somatic cell in a multicellular organism receives a GCR, the organism could develop cancer. Such differences between multi- and uni-cellular organisms could explain why somatic mammalian cells favor non-homologous end joining as the primary mode of DSB repair, whereas vegetative yeast primarily use homologous recombination mechanisms such as SDSA (e.g. Guirouilh-Barbat et al., 2004; Mao et al., 2008).

The mammalian genome appears to have accommodated widespread repetitive elements by providing each chromosome a specific domain. However, in the more tightly packed yeast nucleus, individual chromosomes are in intimate contact, which could explain why yeast have a limited number of repetitive elements in its genome (Tanizawa and Noma, 2011; Duan et al., 2010; Figure 6A). For mammalian genomes, perhaps the positive functions provided by repetitive sequences (e.g. their presence in centromeric, telomeric and ribosomal DNA) are worth the risk of a rare NAHR event. Such a fitness cost could also be offset by a greater chance for genetic variability because the opportunity for recombination is restricted to prevent GCRs.

Here, we illustrate that multiple redundant forms of regulation - early and late recombination mechanisms, cell cycle control, and chromosome organization - collaborate to ensure the stability of repetitive DNA. Because of the essential nature of genome maintenance in adaptive evolution and prevention of disease, these mechanisms are likely to act redundantly. Support of this idea comes from analysis of chromosome stability in MMR-defective human and yeast cell lines. While specific assays have been used to show critical roles for MMR in preventing NAHR, MMR defective lines are in fact karyotypically stable (Heck et al., 2006; Snijders et al., 2003). However, it is likely that such redundant mechanisms are disrupted in some cancers where hundreds to thousands of GCRs can exist within a single tumor (Chen J-M et al., 2010; Stratton et al., 2009; Velculescu 2008).

Of the mechanisms discussed, genome organization may have the most important role in maintaining stability of repetitive DNA and genome stability in general. Large perturbations in genome organization could conceivably disrupt sequestered repetitive elements and compromise other genome protection mechanisms as well. In support of this, mutations within genes that establish and maintain global genome structure – cohesins, condensins, histone acetylases, histone deacetylases, and histone methylases – can cause massive genome instability that is suggested to drive some cancers (Strunnikov, 2010; Fraga and Esteller, 2005). In some cases, such as in the presence of condensin dysfunction, distinct regions of repetitive DNA can become more sensitive to breakage, increasing the opportunity for NAHR (Samoshkin et al., 2011). Beyond genome organization, the relative importance of the specific mechanisms that ensure stability of repetitive DNA will depend on the type of DNA damage, when it occurs during the cell cycle, and the relative importance of disrupted genes for the tissue and organism suffering the damage.

Acknowledgments

We are grateful to members of the Alani lab and Amy Lyndaker for helpful discussions.

Abbreviations

GCR	gross chromosomal rearrangement
KB	kilobases
NAHR	non-allelic homologous recombination
DSB	double-strand break
DSBR	double-strand break repair
SDSA	synthesis-dependent strand annealing
BIR	break-induced replication
SSA	single strand annealing

ssDNA	single-stranded DNA
dsDNA	double-stranded DNA
NHEJ	non-homologous end-joining
MEPS	minimal efficient processing segment
MMR	mismatch repair

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Figure 1.

(A) Types of repetitive DNA sequences are illustrated on two hypothetical chromosomes (blue and red): segmental duplications (green boxes), interspersed repeats (black boxes), satellites (yellow lines) present in eukaryotic genomes and NAHR events that involve repetitive sequences. These include interchromosomal (X), intrachromosomal and intersister rearrangements (curved X). (B) Types of GCRs resulting from NAHR in repetitive sequences. Interchromosomal rearrangements can result in gene conversions (non-crossovers), translocations (crossovers), or unstable acentric or dicentric chromosomes (crossovers, not shown). Intrachromosomal or intersister rearrangements surrounding a chromosomal locus (white arrow) can result in duplications, deletions, or inversions. A color version of the figure is available online.

Figure 2. Recombination mechanisms (DSBR, SDSA, BIR and SSA) that can use repetitive DNA sequences as substrates. (A) DSBR and (B) BIR can result in crossovers and non-crossovers, SDSA (C) creates only non-crossovers, and SSA (D) creates only deletions or chromosome fusions (not shown). See the text for further details. A color version of the figure is available online.

Figure 3.

Model for how NAHR is initiated during replication. **(A)** Repetitive sequences form secondary structures that block progression of the replication fork and induce fork reversal which can result in sequence duplications. Physical stress on a stalled replication fork can also cause breakage of the fork (a DSB) and subsequent repair by homologous recombination (not shown). **(B)** Replication across single-strand gaps may also produce DSBs that may initiate homologous recombination by using the adjacent sister chromatid as a template. A color version of the figure is available online.

Model for heteroduplex rejection during SSA

Figure 4.

A model for how mismatch and double-strand break repair factors can collaborate to reject recombination between divergent DNA sequences during SSA. After annealing of divergent sequences, Msh proteins (i.e. Msh2-Msh6, pink ovals) can recognize base mismatches (red star) in the heteroduplex intermediate and changes conformation to begin a search for Sgs1-Top3-Rmi1 (yellow oval, light green oval, blue oval). Sgs1-Top3-Rmi1 can load onto the junction between the heteroduplex and the 3' non-homologous tail and is stimulated by Msh2-Msh6 to unwind the duplex. A color version of the figure is available online.

Model for rejection of a heteroduplex in a D-loop

Figure 5.

Heteroduplex rejection within a D-loop. Similarly to rejection during SSA (Figure 4), Msh2-Msh6 (pink ovals) will locate a mismatch (red star) and switch to searching mode. Msh2-Msh6 may either (1.) find Sgs1-Top3-Rmi1 (yellow oval, light green oval, blue oval, or another helicase such as Srs2, not shown) loaded at the duplex junction to stimulate unwinding, or instead may (2.) find an active replication fork (represented as Pol δ, purple hexagon) through a direct interaction with PCNA (dark blue square) to stimulate nucleolytic degradation. In a third alternative (3.), Mlh1-Pms1 (dark green ring) may accompany activated Msh2-Msh6 during the search and may recruit an exonuclease such as Exo1 (blue pac-man) to either stimulate repair of the mismatch, or to disrupt the D-loop by a nucleolytic mechanism. A color version of the figure is available online.

Figure 6.

(A) Model for the nuclear organization of chromatin in mammalian and budding yeast nuclei. Fractal-globule models (Mirny, 2011) predict that individual chromosomes (distinguished by color) in mammalian nuclei (left) are folded into distinct, untangled territories with heterochromatin domains associated with the nuclear lamina and euchromatin in the center of the nucleus. The nucleolus is a distinct heterochromatin domain that houses ribosomal DNA which is distributed among multiple chromosomes in humans. The yeast nucleus (right), which is 100 times smaller than an average mammalian nucleus (3 versus $300 \mu\text{m}^3$), is predicted to be less tolerable of a fractal globule model so that chromosomal territories are more closely entwined. 3C modeling by Duan et al., (2010) show protrusion of the rDNA locus on chromosome 12 into a distinct heterochromatin domain and also clustering of other heterochromatin regions such as centromeres and telomeres. (B) Heterochromatin is more compact than euchromatin and is associated with specific marks such as methylated (Me) histones and HP1 protein. Histones in euchromatin are usually acetylated (Ac). Nucleosomes (purple circles). A color version of the figure is available online.

Figure 7.

(A) DSB repair by homologous recombination requires chromatin modifications and nucleosome remodeling within approximately 50 KB on each side of the DSB to facilitate loading of HR proteins that are excluded from heterochromatin (i.e. Rad51 and Rad52). During S and G2 phase, break-induced loading of cohesin (orange lines) occurs within the region of the DSB to facilitate sister chromatid recombination and this is dependent on γ H2AX (yellow stars) and the resection initiator MRX (not shown). This panel is based on Figure 2 of Lee and Myung (2009). (B) Model for movement of DSBs within heterochromatin to the heterochromatin periphery, as described by Chiolo et al., (2010). DSBs (yellow) within heterochromatin domains (gray) move, by an unknown mechanism, toward the periphery of the heterochromatin (dotted line) accompanied by a global expansion of the heterochromatin domain. Finally, DSBs protrude into the euchromatin domain (light blue) where the Rad51 protein (red) is available for homologous recombination. A color version of the figure is available online.