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The Relationship Between Replication and Recombination

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1. Inroduction

DNA replication, the process of copying double-stranded DNA, and DNA recombination, the process of breaking DNA strand and joined to a different strand, are central characteristics of life. The aim of this chapter is to discuss the relationship between replication and recombination. Understanding the intimate links between these processes gives us a more holistic approach to understanding the functioning of a cell.

Replication and recombination machineries cooperate to maintain biological inheritance and genomic integrity. While replication enables the formation of two identical DNA molecules from a single double-stranded DNA, recombination enables accurate repair of errors that occur on both strands of DNA as well as the formation of new combinations of genes. Recombination can occur between similar molecules of DNA (homologous recombination), or dissimilar molecules (non-homologous end joining). Homologous recombination predominantly occurs during and shortly after DNA replication (late S and G2), while non-homologous end joining is predominant in the G1 and early S phase of the cell cycle.

What is the relationship between DNA replication and recombination processes? Mutations in some genes with a role in DNA replication cause hyper-recombination phenotypes. These mutations require recombination protein Rad52 for their viability, suggesting that the replication errors caused by mutations are repaired by recombination mechanisms (Merrill & Holm, 1998). Furthermore, many recombination genes have S phase defects when deleted. Obviously, replication and recombination processes are tightly intertwined. In this chapter I will try to present the close coupling between these processes from a different point of view (Fig. 1): recombination is part of DNA replication and, vice versa, DNA synthesis is part of the recombination process; both processes are connected via checkpoints; both processes are regulated by common posttranslational modifications; both processes take advantage of double helix DNA and both have a common problem with DNA unfolding.

The recombination system plays a crucial role in DNA replication ensuring that replication machines can complete their task of genome duplication. DNA replication forks stall or collapse at DNA lesions or problematic genomic regions. When a fork becomes stalled, the replisome often remains firmly associated with the fork. But, when replication forks are removed, recombination is the most important rescue mechanism. The recombination mechanism forms substrates for the assembly of a new replication fork thus allowing continued DNA replication.

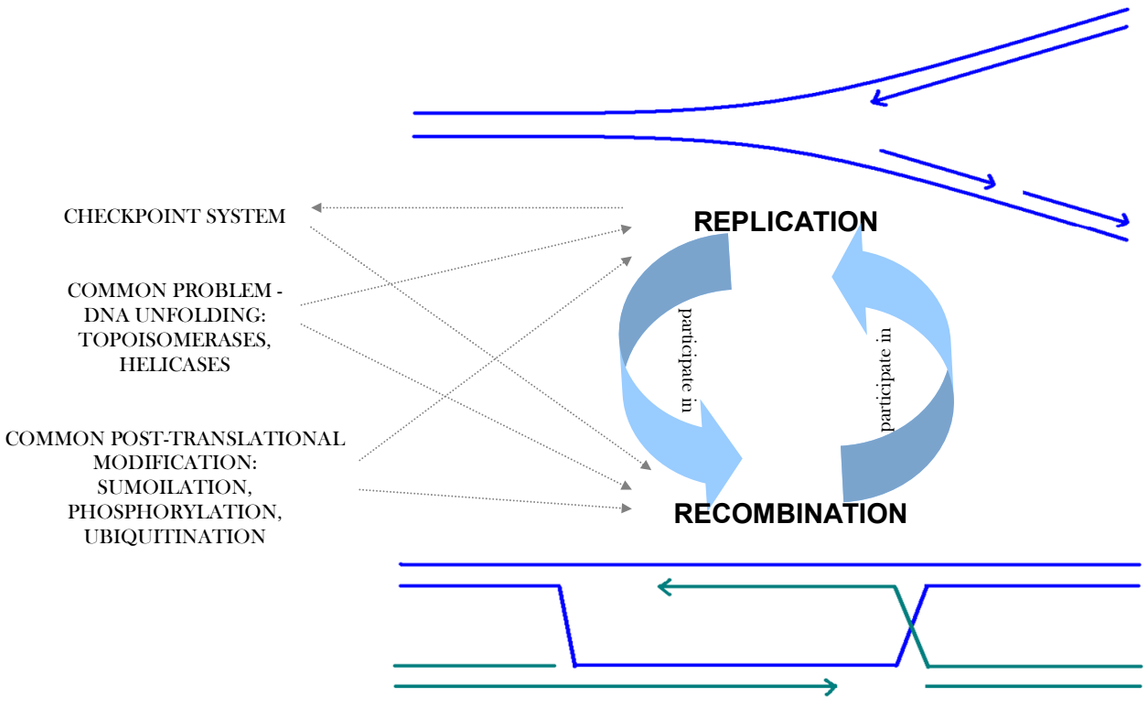

Fig. 1. Replication and recombination processes are tightly intertwined: recombination is part of DNA replication and, vice versa, DNA synthesis is part of the recombination process. They are affected by the common factors: checkpoint, DNA unfolding and post-translational modifications.

DNA synthesis is a crucial step during the recombination process. After Rad51-mediated DNA strand invasion, DNA synthesis is the next step in recombination to restore the integrity of the chromosome. After DNA strand invasion, dissociation of Rad51 is required to allow access for DNA polymerases to prime DNA synthesis at the invading 3′ OH end. Repair DNA synthesis during the recombination process is similar to normal S-phase replication, but has specific properties.

A close coupling between replication and recombination is also demonstrated in the checkpoint system. In addition to sensing DNA damage, the role of the DNA damage checkpoint is also to coordinate cell cycle progression, DNA replication, and DNA repair mechanisms. When forks collapse during replication and generate single-stranded DNA ends, these ends activate the replication checkpoint. Activated replication checkpoint proteins further activate the recombination machinery.

A close coupling between replication and recombination is also demonstrated in common posttranslational modifications. Posttranslational modifications, with their key role in controlling protein function, play an important role in the maintenance of genome integrity. Sumoylation, phosphorylation, and ubiquitination are especially important for the functioning of replication and recombination proteins, allowing them to execute their functions in a rapid and efficient manner.

Replication and recombination mechanisms both take advantage of double helix DNA and have a common problem with DNA unfolding. Both processes take advantage of the complementary base pairing between the strands to undertake their tasks. Each strand of

the duplex provides a template for generating the other strand. When one strand of DNA is damaged, the complementary sister strand can be used as a template to regenerate the damaged strand and recover information encoded in its sequence. However, the organization of DNA sequences into a chromatin structure represents a barrier to replication and recombination processes. Because replication and recombination require access to the sequence in the interior of the double helix DNA, the chromatin structure has to be remodeled during these processes. Both processes require DNA topoisomerase to unwind the DNA helix and DNA helicase to open the DNA helix.

This chapter mostly refers to the basic mechanisms applicable to eukaryotes that have been studied in budding yeast *Saccharomyces cerevisiae. S.cerevisiae* is the best studied eukaryotic model organism that providing the most integrated view of replication and recombination processes. At the end of this chapter, a lesser known yeast protein Ecm11 is discussed, which affects both replication and recombination processes.

2. Recombination during DNA replication

DNA replication represents a sensitive period in the cell cycle because the stretched chromatids and the stability of the replicating forks are highly susceptible to damage. Failure to restart replication accurately would result in serious consequences for organism: accumulation of mutations, enhanced genome instability, or even cell death. Recombination plays a crucial role in DNA replication by ensuring that replication machines can complete their task of genome duplication. DNA replication forks can stall or collapse at DNA lesions or problematic genomic regions. At problematic replication regions, e.g. inverted repeats (Ty elements) and tRNA genes, the replication fork progression is slowed down and fork stalling is a frequent event. When forks are stalled, the replisome often remains stably associated with the fork; Rad53 stabilizes stalled forks by gluing the replisome onto the replicating molecule (Lucca et al., 2004). Resumption of DNA replication can occur when the block is relieved. In other situations, like DNA breaks or unremoved protein-DNA complexes, the replisome dissociates and the fork collapses (Lambert et al., 2005). When replication forks are removed, recombination is the most important rescue mechanism. The recombination process forms substrates for the assembly of a new replication fork. There are also alternatives to a replication restart. Specialized DNA polymerases, translesion polymerases, are able to replicate across sites of DNA damage and allow re-initiation of replication by normal replicative polymerases beyond the lesion (Friedberg et al., 2002). As translesion polymerases are mutagenic, their activation is tightly controlled. It has been shown that translesion synthesis is used only when a recombination mechanism is not available (Berdichevsky et al., 2002).

Replication restart by recombination mechanisms is required when stalled replication forks are processed up to DSBs or at sub-telomeric regions where there are no converging forks that could complete DNA duplication. Cells take advantage of homologous recombination (HR) to create substrates for assembly of a new replication fork. Holliday junctions enable the site of the original lesion to be returned to a duplex formation and become accessible to repair systems. It has been shown that specific nuclear foci of Rad52 are formed during S phase and that each Rad52 focus represents a center of recombinational repair capable of processing DNA lesions (Lisby et al., 2001). Sister chromatids are the preferred partner for DSB repair in mitotic diploid yeast cells. It was confirmed that cohesion between sister chromatids is essential for efficient DSB repair in mitotic cells (Uhlmann, 2001). A major

damage tolerance pathway involving recombination is the template switch, which uses the information on the sister chromatid in the proximity of replication forks. Homologous recombination factors and DNA polymerase δ promote the formation of template switch intermediates. These intermediates are dissolved by the action of the Sgs1 helicase in association with the Top3 topoisomerase rather than by Holliday Junction nucleases (Vanoli et al., 2010). Another recombination mechanism, which has been implicated in the restart of collapsed forks, is break-induced replication (BIR). BIR is an efficient homologous recombination pathway repairing a DNA double-strand break when only one of two ends of the DSB succeeds in strand invasion of a homologous sequence. This recombination pathway includes the synthesis of a long tract of DNA that can be attributed to recombination-directed DNA replication and is discussed in the section about replication during the recombination process (section 3.3.).

2.1 Replication checkpoint is linked to recombination machinery

DNA damage is constantly being sensed by sophisticated cellular networks - DNA damage checkpoints. This is because genome integrity is continuously challenged by DNA lesions, DNA single-strand breaks (SSBs) and double-strand breaks (DSBs). DNA damage and replication checkpoint proteins monitor genome integrity, recognize different forms of DNA damage, transduce appropriate signals, initiate DNA repair, and slow the progression of the cell cycle to allow DNA repair to occur (Boddy & Russell, 2001). At critical stages before or during DNA replication (G1/S and intra-S checkpoints) and before cell division (G2/M checkpoint), the checkpoint proteins delay or stop the cell cycle if DNA damage is unrepaired to prevent duplication and segregation of damaged DNA. A network of checkpoint proteins is tightly coordinated with cell cycle progression. Besides its acting in cell cycle arrest, the checkpoint response is linked to activation of the repair and recombination machinery (Zhou & Elledge, 2000). Thus, the role of the checkpoint system is very complex, in that it senses the DNA damage while also coordinating cell cycle progression, DNA replication and DNA repair mechanisms. The functioning of replication proteins, recombination proteins, and checkpoint proteins is closely intertwined.

During DNA replication, stalled forks generate single-stranded DNA ends coated with replication protein A (RPA), which activates the replication checkpoint. It has been shown that a significant amount of ssDNA must be exposed in order to activate the checkpoint response (Shimada et al., 2002). Activated replication checkpoint proteins further protect the stability of stalled replication forks (Lopes et al., 2001) or activate recombination machinery when forks collapse.

A central transducer of checkpoint proteins is the kinase Mec1 (hATR), which is recruited to stalled forks and probably activated in response to signals generated by the clamp-sensor in the presence of DNA damage (Boddy & Russell, 2001). Activated Mec1 phosphorylates Mrc1, a protein required for replisome stabilization and checkpoint activation (Katou et al., 2003). Kinase Tel1 (hATM) is also a component of the common signalling pathway and has a role similar to Mec1. Mec1 and Tel1 both phosphorylate serines and threonines on numerous target proteins, e.g. H2A, in response to DNA damage (Downs et al., 2000). Downstream from Mec1, the Rad53 kinase responds to DNA replication arrest. Rad53 is a conserved protein directly affecting replication fork stability. Mec1 and Tel1 phosphorylate Rad53 and Mrc1. Phosphorylated Mrc1 binds the fork-associated hyperphosphorylated Rad53, leading to its activation (Alcasabas et al., 2001). Kinase Rad53 phosphorylates and activates other protein kinases that induce other processes that enable repair of the damage.

The similarity between checkpoint sensors and replication proteins has been pointed out (Forsburg, 2002). One of the checkpoint complexes is a specialized version of the replication clamp-loader RFC, with the large subunit replaced by a checkpoint-specific protein Rad24. There is also a checkpoint version of the clamp related to PCNA (processivity clamp of DNA polymerases), Mec3-Rad17-Ddc1. Those proteins act as checkpoint sensors of damage and as effectors of DNA repair.

2.2 Sister chromatid cohesion is coupled to DNA replication

Cohesins are ring-shaped complexes made up of Scc1, Scc3, Smc1, Smc3, and Pds5 subunits. Smc1 and Smc3 are structural maintenance of chromosome (SMC) proteins with ATPase domains. Cohesins keep the sister chromatids connected with each other, they facilitate spindle attachment onto chromosomes during metaphase, and their presence is essential for the proper transmission of sister chromatids to dividing daughter cells.

Cohesins between sister chromatids, recombination, and replication are closely intertwined processes. The sister chromatid cohesion complex plays a crucial role in DNA damage repair by recombination mechanisms, however sister chromatid cohesion is also coupled to DNA replication. Cohesins are loaded onto chromatin before DNA replication. Establishment of cohesion between sister chromatids is coupled to DNA replication and requires the active participation of replication fork and other replication-related activities (Carson & Christman, 2001). It has been shown that proper cohesion require PCNA - a processivity clamp for DNA polymerases, Pol σ - an essential DNA polymerase, Replication Factor C (RFC) - a clamp–loader complex, and cohesion establishment factors. It has also been shown that fork progression itself is tied to cohesin acetylation (Sherwood et al., 2010). The most important cohesion establishment factor is Eco1/Ctf7 acetyltransferase. The mutation of cohesion factor *eco1* can be suppressed by overexpression of PCNA (processivity factor for some DNA polymerases), suggesting that cohesion during the S-phase might actually be mediated by replication fork components (Skibbens et al., 1999). It has also been shown that Eco1 physically interacts with all RFC complexes (Kenna & Skibbens, 2003). As Eco1 is essential for cohesion establishment and the RFC complex is a replication clamp loader that loads PCNA onto dsDNA and promote processive DNA replication, these interactions provide new evidence regarding linkage between cohesion establishment and DNA replication. Other links between the replication machinery and the cohesion machinery are DNA polymerase Trf4/Polσ and components of the replisome progression complex (RPC). Because defects in *trf4* mutants result in a failure of cohesion between the replicated sister chromatids, it was concluded that Trf4/Polσ is required to establish cohesion during S-phase (Wang et al., 2000).

While the multiprotein cohesion complexes depend on loading and establishment factors that are intimately connected to DNA replication, it has also been shown that cohesion establishment factors are implicated in maintaining the processivity and stability of replication forks (Branzei & Foiani, 2010). Interaction between replication forks and cohesin rings stabilize replication forks and/or enable sister chromatid-dependent restart pathways. Some of the components, such as the Tof1–Csm3 complex and Mrc1, appear to be involved in maintaining fork integrity and are recognized as components of the replication checkpoint (Katou et al., 2003). On the other hand, Tof1–Csm3 complex and Mrc1 are implicated in sister chromatid cohesion (Mayer et al., 2004; Xu et al., 2004).

In conclusion, DNA replication and cohesion establishment are intimately coordinated (Sherwood et al., 2010): replication forks, travelling along the DNA, modify cohesin's

architecture and association with chromatin, and on the other hand, cohesion in turn affects the dynamics of DNA replication and keeps the sister chromatids connected to each other.

3. DNA synthesis during recombination

3.1 Recombination process

For the cell, it is essential that DNA breaks are repaired promptly to prevent chromosomal aberrations or cell death. Recombination is a key pathway to preserve genomic stability by repairing DNA breaks, gaps, and interstrand crosslinks. Recombination is an essential DNA repair process, particularly for the repair of DNA-double strand breaks (DSBs). The potentially, very dangerous DSBs are repaired by different recombination pathways: non-homologous end joining (NHEJ), single-strand annealing (SSA), break-induced replication (BIR; outcome is half-crossover), synthesis-dependent strand annealing (SDSA; outcome is noncrossover), and double Holliday junction pathways (dHJ; outcome is crossover or noncrossover). In yeast cells, DSBs are generally repaired by noncrossover/gene conversion pathways. The first two pathways, NHEJ and SSA, can occur within one molecule of DNA. DSB resection is a required step in SSA as in HR, but not in NHEJ where DNA end-binding factors Ku70-Ku80 inhibit DSB resection (Tomita et al., 2003). NHEJ is favoured over SSA and HR in G1 phase.

The last three pathways (dHJ pathways, SDSA, BIR) are template dependent processes involving another molecule of DNA, a sister chromatid or a chromosome. They are assigned to homologous recombination pathways (HR) that require Rad52 and Rad51. In the first phase of HR, DNA damage is processed to form a single-strand DNA (ssDNA) region that is bound by ssDNA-binding replication protein A (RPA). RPA has an important role during recombination. Its primary role is to antagonize secondary structures in the ssDNA and favor formation of the active Rad51-ssDNA filament. Besides that function, RPA is able to bind the displaced strand in the D-loop and stabilize the invasion intermediate (Eggler et al., 2002). In the second phase, the Rad51-ssDNA filament performs a homology search and invades the donor DNA strand. The displacement loop (D-loop) is formed and within the D-loop the invading strand primes DNA synthesis. Motor protein Rad54 enhances D-loop formation by Rad51. In the third phase, the pathways of HR are distinguished. Subpathways of HR require specific protein cascades that have been only partially defined to date (Heyer et al., 2010):

- When only one homologous DNA strand is found, the D-loop is converted to a replication fork and cell choose the BIR pathway of repair. This process enables the repair of the chromosome, but leads to loss of heterozygosity of genetic information distal to the DSB.
- When both ends of the break interact with homologous sequences that are used as a template for repair, the predominant pathway for DSB repair is SDSA. The D-loop is reversed and allows the annealing of the newly synthesized strand with the resected strand of the donor end. This pathway avoids crossovers and reduces potential genomic rearrangements.
- Double Holliday junction pathways with crossover or noncrossover outcome are prone to noncrossover products in the vegetative cell cycle. Crossovers are primarily intended for meiotic formation of new combinations of genes. In vegetative cells, DNA repair is infrequently associated with crossovers, because crossovers can lead to deletions, inversions, or translocations when non-allelic or repeated sequences are present.

3.2 Chromatid cohesion and recombination mechanisms

Recombination mechanisms use a genetically similar DNA molecule, usually the sister chromatid, to repair damaged DNA and maintain the original sequence information. The sister chromatid cohesion complex plays an important role in DNA damage repair by recombination mechanisms, because cohesin holds the broken chromatid in close proximity to its intact sister chromatid, thereby supporting efficient repair. On formation of DSBs, cohesin even accumulates and forms new cohesive structures on chromatin that surrounds the break site. The ability of cohesin to establish new cohesion structures is essential for its role in DNA damage repair, possibly by physically stabilizing fragmented parts of the chromosome. Accumulation of cohesin is controlled by the DNA damage response and cohesin-regulating factors. Cohesion formation is limited to the S phase of the cell cycle, but DSBs can also trigger cohesion after DNA replication has been completed (Strom et al., 2007). It has been shown that damage-induced cohesion is also essential for recombinational repair in postreplicative cells. Cohesion is established genome-wide after induction of a single DSB. Thus, a cohesion establishment pathway exists that is independent of DNA duplication but required for DNA repair. Cohesin may act as a platform for the recruitment of checkpoint and DNA repair proteins and helps to translate checkpoint signals into DNA repair.

3.3 DNA synthesis during the recombination process

DNA synthesis is a part of the recombination process. After Rad51-mediated DNA strand invasion, DNA synthesis is a crucial step in recombination to restore the integrity of the chromosome. Motor protein Rad54, which stimulates D-loop formation, also promotes the dissociation of Rad51 from the heteroduplex after DNA strand invasion (Kiianitsa et al., 2006). Dissociation of Rad51 is required to allow access for DNA polymerases to prime DNA synthesis at the invading 3′ OH end. Repair DNA synthesis during the recombination process is similar to normal S-phase replication, but has specific properties:

- The DNA polymerases required for DNA synthesis in homologous recombination remain to be defined; DNA polymerases Pol δ (Lydeard et al., 2007; Maloisel et al., 2008) and Pol η (McIlwraith et al., 2005) have been proposed.
- Recently it was shown that PCNA, the sliding clamp that locks DNA polymerase onto dsDNA and promotes processive DNA replication, has a specific role in the initiation of recombination-associated DNA synthesis (Li et al., 2009). It was shown that PCNA is required for Pol δ recruiting to a D-loop and the extension of the 3'-end of the invading strand. PCNA and RFC are essential even to synthesize as little as 30 nucleotides following strand invasion (Holmes & Haber, 1999).
- DSB-induced gene conversion does not require lagging-strand components like Polα-primase complex and Cdc45, which is responsible for loading the Polα-primase complex onto chromatin during DNA replication (Wang et al., 2004). It has been proposed that new DNA synthesis is initiated through the leading-strand, using the 3′ end that was generated by resection, and that Rad51-mediated strand invasion is used as the primer end with primase activity. On the other hand, BIR do require lagging-strand components and major replicative DNA polymerases.
- Recombination mediated replication does not require initiation replication proteins or additional MCM (Minichromosome Maintenance complex) loading. Normal DNA replication requires formation of a pre-RC (pre-replicative complex) in early G_1. Cdc6

and Cdt1 bind to the chromatin binding ORC (origin recognition complex) and enable the recruitment of Mcm2-7. Cdc6 accumulates at the end of mitosis and disappears after the initiation of DNA replication, and Cdt1 accumulates in the nucleus during G_1 and is excluded from the nucleus for the rest of the cell cycle to prevent second-round replication. Furthermore, Mcm proteins are largely excluded from the nucleus in G_2 phase. Thus, ORC and pre-RC should not be required for DSB repair. This hypothesis was confirmed in DSB-induced gene conversion during *MAT* switching (Wang et al., 2004).

- DNA repair synthesis is not as efficient and processive as normal replication. The explanation for this reduced efficiency could be the lack of processive Mcm helicase.

3.4 Break induced replication

DSB repair by homologous recombination most often involves only a short section of new DNA synthesis. On the other hand, the BIR homologous recombination pathway includes the synthesis of very long tract of DNA; therefore, this pathway can be attributed to recombination-directed DNA replication. Break induced replication (BIR) is a homologous recombination pathway that is able to repair a DNA double strand break (DSB) when homology is restricted to one end. Recombination enables the formation of a unidirectional replication fork that leads to extensive replication and copies the donor chromatid to the end of the chromosome.

BIR requires leading and lagging strand replication machinery, all three major replicative DNA polymerases, including the otherwise nonessential Pol3 (subunit of Polδ), and recombination proteins Rad51 and Rad52. In contrast to other HR pathways, BIR also requires Cdc45, GINS, and Mcm2-7 that form the functional replicative DNA helicase; and initiation factor Cdt1 that recruits Mcm2-7 to the pre-RC (Lydeard et al., 2010). The origin recognition complex (ORC) and Cdc6, parts of the pre-replication complex (pre-RC) are not required, while initiation replication protein Cdc7 is required for BIR. BIR is an effective repair mechanism, characterized by origin-independent and recombination-dependent replication. The posttranslational modifications sumoylation and ubiquitination, have a special role in BIR. Siz1 mediated sumoylation and Rad18-mediated ubiquitination of the processivity clamp PCNA are involved in BIR, but not in gene conversion.

BIR can occur outside of the S phase (Bosco & Haber, 1998), but it is not yet known how replication machinery is then formed. In BIR, Mcm2-7 and Cdt1 have to cope with a single recombination fork, while outside of the S phase they are exported from the nucleus or degraded to prevent reinitiation of replication.

3.5 Replication and recombination in a radiation-resistant organism

Bacteria *Deinococcus radiodurans* is one of the most radiation-resistant organisms yet discovered. It is capable of surviving extremely high doses of acute (10,000 Gy) and chronic (60 Gy/hour) ionizing radiation and it is resistant to other DNA damaging conditions including exposure to desiccation, ultraviolet (UV) light, and hydrogen peroxide. It has been shown that the extraordinary robustness of *D.radiodurans* depends on efficient proteome protection (Krisko & Radman, 2010). Beside manganese accumulation and specific protein protection, survival depends on the efficient and rapid reconstitution of a functional genome from numerous DNA fragments. Recombinational repair with extensive DNA synthesis is used (Slade et al., 2009). DNA repair is primed by recombination proteins RecA and RadA,

while the elongation step is performed by Pol III and PolI. Pol III activity appears to be a prerequisite for initiating DNA repair synthesis, whereas Pol I enables its continuation. Deinococcus radiodurans has more complementary or homologous DNA fragments to engage as repair partners, but otherwise the steps of repair are conspicuously normal (Galhardo & Rosenberg, 2009). The key repair mechanism is the combination of long tracts of newly synthesized DNA and homologous recombination.

4. Meiosis

The meiotic cell cycle in nature does not happen as often as vegetative cell cycle, but is even more special, difficult, and controlled. Meiosis is a complex developmental program that leads to the generation of haploid spores (gametes) from diploid cells. The central feature of meiosis is homologue pairing and meiotic interhomologue recombination that is enabled by meiosis-specific factors. After chromosome pairing and recombination, two successive segregations occur: MI is a reductional division, in which homologous chromosomes segregate and MII is an equational division, in which sister chromatid segregate. Meiotic recombination is essential for proper chromosome segregation at MI where homologous chromosomes are synapsed and then distributed to opposite poles.

4.1 Meiotic replication

It has been known for a long time that cohesion between homologs, which is essential for crossing over, is established during meiotic replication and that the length of meiotic replication is modified by recombination factors like Spo11 and Rec8. Recombination initiation is directly linked to meiotic replication. It has been shown that delaying meiotic replication also delays specific meiotic break formation and it has been suggested that DSB formation occurs as part of the process initiated by DNA replication (Borde et al., 2000). These facts lead to the conclusion that meiotic replication plays a fundamental role in the meiotic recombination process.

The meiotic replication program is generally quite similar to that of the vegetative cell cycle: the same origins of replication and the same replicative machinery are used (Budd et al., 1989). But there are specific features that distinguish mitotic and meiotic replication. The most noticeable feature is a protracted meiotic replication that is universally several times longer than mitotic replication in the same organisms. The difference has been proposed to be related to the process of laying down specialized chromosome features utilized at later stages for interhomolog interactions; the progression of the S-phase might be directly coupled to this (Cha et al., 2000). Pairing of homologues is a complex process that is essential in meiosis but not required in mitosis; thus, it is not surprising that DNA replication and preparing for the next phase in meiosis takes more time.

4.1.1 Mum2 in meiosis

The study of the Mum2 protein reveals a direct correlation between the level of meiotic DSBs and DNA replication (Davis et al., 2001), which was suggested on the basis of the observation that a delay in replication results in a similar delay in DSB formation (Borde et al., 2000). Mum2 is essential for meiotic replication, but it is not required for mitotic DNA replication. Its role in meiotic replication is not clear; however, synthetic interactions with the ORC complex and polymerase α-primase suggest that it is involved in the functioning of

the replication machinery. It was shown that in *mum2* mutants, chromosome pairing and synapsis occur, although at reduced levels compared to wild type, but meiotic recombination is greatly impaired. Meiotic gene expression, pairing, and synapsis were only partly reduced in *mum2* mutants, thus it was suggested that the reduction in DNA replication is directly responsible for the reduced level of DSBs and meiotic recombination (Davis et al., 2001).

4.1.2 Ime2 in meiotic replication

Ime2 is an essential meiotic protein that links DNA replication with the following phases of the meiotic cell cycle that follow it. IME2 belongs to early meiotic genes that are regulated by Ime1, while Ime2 is the key protein for the transcription of the middle genes. The transcription of the late genes is indirectly dependent on Ime1, Ime2, and Ndt80. The early genes are those which encode proteins involved in DNA replication, synapsis of homologs and meiotic recombination, whereas the middle genes encode proteins required for nuclear division and spore formation. Correlation between meiotic DNA replication and nuclear division is regulated by an early meiosis-specific gene. Ime2, which controls both initiation of premeiotic DNA replication and the transcription of *NDT80*, has a key role in the correlation between premeiotic DNA replication and nuclear division. It was also demonstrated that Ime2 functions as a negative regulator of Clb-Cdc28 (Gurevich & Kassir, 2010).

4.1.3 Clb5,Clb6–Cdc28 in meiotic replication

Many proteins with a role in meiotic replication and recombination are phosphorylated suggesting that kinases could play an important role in coordinating both processes. Kinases Clb5,6-Cdc28 and Cdc7-Dbf4, which initiate meiotic replication and DSB formation could have a key coordination role (Wan et al., 2008).

Clb5,Clb6–cyclin-dependent kinase (Clb5,6-Cdc28) is the principal activator of the S phase in the vegetative cell cycle, but the absence of Clb5 and Clb6 confers only a delay in the initiation of replication. They are replaced by functionally related B-type cyclins Clb1 and Clb4 (Schwob et al., 1994). In contrast, Clb5 and Clb6 are essential for the initiation of meiotic replication; in the *clb5clb6* double mutant, meiotic replication is not detectable (Stuart & Wittenberg, 1998). Beside its role in initiating DNA replication, Clb5,6-Cdc28 also has a crucial role in the promotion of DSB formation in meiosis. Mutants *clb5* and *clb5clb6* but not *clb6* are defective in DSB induction and SC formation (Smith et al., 2001). DSBs are formed by Spo11 protein and accessory factors like Mer2. It has been shown that Clb5,6-Cdc28 phosphorylate Mer2 and that this phosphorylation modulates interactions of Mer2 with other DSB proteins and is critical for DSB formation (Henderson et al., 2006).

4.1.4 Cdc7 kinase in meiosis

Cdc7 is an essential kinase that forms complexes with the regulator Dbf4, the levels of which fluctuate during the cell cycle. Cdc7 is a key regulator of meiosis, because it is required for the initiation of DNA replication, for meiotic recombination, for regulation of the *NDT80* promoter, and for proper recruitment to kinetochores.

In the vegetative cell cycle, phosphorylation of the MCM complex by Cdc7p-Dbf4 activates DNA replication. Loss of Cdc7 function affects initiation at all origins, even at late origins (Bousset & Diffley, 1998). An allosteric model has been proposed in which phosphorylation

of Mcm2 by Cdc7p-Dbf4 confers an allosteric change on Mcm5p and produces an active, 'rolling' MCM helicase that can move with the replication fork (Sclafani, 2000). As in mitosis, the Cdc7-Dbf4 complex is essential for initiation of DNA replication during meiosis (Valentin et al., 2006).

Besides the role in initiation of meiotic replication, Cdc7 kinase also has a role in the meiotic recombination. It has been shown that Cdc7 is essential for meiotic DSBs and meiosis I progression. Cdc7 enables phosphorylation of the DSB protein, Mer2. It has been proposed that Cdc7 regulates Spo11 loading to DSBs by Mer2 phosphorylation (Sasanuma et al., 2008). In meosis, Cdc7 kinase also provides the link between replication and chromosome segregation. It has been shown that Cdc7 promotes meiotic progression by enabling transcription of *NDT80*; in addition it is required for mono-orientation of sister kinetochores in MI by allowing recruitment of the monopolin subunit, Mam1, onto kinetochores (Lo et al., 2008).

4.2 Recombination in meiosis

The unique features of meiosis are homologue pairing and inter-homologue recombination that is initiated by double-strand breaks. The specific feature of meiotic recombination is the presence of meiosis-specific factors that influence the mitotic recombination machinery to use the homologous chromosome instead of a sister-chromatid as the recombination template and to counteract mitotic favorization of non-crossover outcomes.

Meiotic recombination occurs during the extended prophase. In contrast to mitotic recombination, meiotic recombination is genetically programmed and induced by Spo11-catalyzed DSBs. Therefore, in meiosis there is an additional source of DSBs that requires active recombination to be resolved. DSBs are resected to expose 3' single strand overhangs by the Mre11-Rad50-Xrs2 complex and endonuclease Sae2. Overhangs of ssDNA can load Rad51 and meiosis-specific recombinase Dmc1 to form nucleoprotein filaments that catalyze strand invasion on the homologous chromosome (Hayase et al., 2004). In contrast to mitotic cells, meiosis-initiated DSBs are repaired using the homologous chromosome, not the sister chromatid, as a template for repair. Strand invasion generates DNA synthesis and ligation that result in the formation of double Holliday junction structures (dHJ). dHJ generated between homologs are resolved by structure-specific endonucleases. Homologous recombination products (crossovers and non-crossovers) are formed. While crossovers (Cos) absolutely require double a Holliday junction (dHJ) intermediate, non-crossovers (NCOs) can occur by synthesis-dependent strand annealing (SDS) or by special cleavage of dHJ. The resolution of dHJ depends on structure-specific endonucleases. COs preferentially occur at hot spots that are influenced by DNA sequence and higher order chromosome structures, but are strongly suppressed in large chromosomal regions near the telomeres, centromeres, rRNA genes, and Ty elements (Petes, 2001). COs are associated with reciprocal exchanges of chromosome arms and promote accurate chromosome segregation in MI, while non-crossovers are not. Because of its key role in meiosis, crossover outcome is tightly controlled. At least one CO is formed per chromosome pair and a crossover in one region makes it less likely that another will be found nearby (crossover interference). The COs/NCOs ratio can change to maintain COs. It has been shown that COs tend to be maintained in *spo11* mutants with reduced DSBs at the expense of NCOs (Martini et al., 2006). Spo11 is loaded to DNA after homolog pairing; therefore, crossover control is likely based in earlier processes.

It has been shown that noncrossover products are formed at the same time as dHJ intermediates, while crossovers appear later, when dHJ intermediates are resolved (Allers &

Lichten, 2001). *ndt80* mutants arrest with unresolved dHJ intermediates and very few crossovers, while noncrossover heteroduplex products are formed at normal levels and with normal timing. These results suggest that crossovers are formed by resolution of dHJ intermediates, while most noncrossover recombinants arise by a different, earlier pathway and that dHJ resolution is under control of meiosis-specific transcription factor Ndt80. Noncrossover recombinants are most probably formed by SDSA, where the invading strand is not captured but is instead displaced. The other possibility is that dHJ intermediates are differentiated at an early stage and intermediates of noncrossovers are resolved very rapidly. The latter pathway of noncrossover formation through dHJ is less possible and cells probably use it only as an alternative pathway when crossovers could not be carried out.

4.2.1 ZMM proteins

ZMM proteins are components of SC (Zip1, Zip2, Zip3, Zip4), mutS homologues (Msh4, Msh5), and meoisis specific DNA helicase Mer3 (Borner et al., 2004). ZMM proteins play a crucial role in crossover formation; despite efficient initiation of recombination, crossovers are reduced or absent in *zmm* mutants. Elimination of crossovers is not due to reduced DSBs formation, because DSBs accumulate to wild-type levels in *zmm* mutants. The formation of NCOc is independent of ZMM proteins. Thus, ZMM are specifically required for formation of COs. ZMM proteins interact with recombination proteins, e.g. Mre11, Rad51, and Rad57 (Agarwal & Roeder, 2000). In meiosis there are two types of COs: one type of CO that is dependent on the activities of ZMM proteins and a second type of CO that is ZMM-independent. COs are not randomly assigned, but mostly they do not occur in adjacent chromosomal regions; this property is called CO-interference. The ZMM-dependent COs represent the majority of COs in yeast and are subject to interference, while ZMM-independent COs do not exhibit interference.

ZMM proteins are essential for the assembly of SC formation; Zip1 is an integral component of the SC. They play an important role in coordination between molecular recombination events and assembly of the SC.

The exact function of ZMM proteins in meiosis still remains to be clarified; although they probably affect strand invasion.

4.2.2 Synaptonemal complex

Meiotic recombination depends on the development of the meiosis-specific chromosome structure synaptonemal complex (SC). SC is a protein network that pairs homolog chromosomes along their entire length and holds them together. The cohesion complex consists of one filament (lateral elements) on each homologue and central elements linking lateral elements a in ladder like structure. Central elements contain various proteins, including Zip1 (Sym et al., 1993) and SUMO (Cheng et al., 2006). Lateral elements contain meiosis-specific proteins, e.g. Red1, Hop1, Mek1/Mre4, and a cohesion complex that is similar to the mitotic sister chromatid cohesion complex, only that SCC1 is replaced by Rec8 in meiosis (Xu et al., 2005). It has been shown that meiosis-specific kinase Mek1 suppresses meiotic intersister DSB repair by working directly on sister chromatids and that Mek1 acts on Rad51-specific recombination processes (Callender & Hollingsworth, 2010).

4.2.3 Cdc28 in meiotic recombination

Most components of SCs including Zip1, Hop1, Red1, Mre4, and Rec8 are phosphoproteins, although the functional significance of this phosphorylation remains to be characterized

(Zhu et al., 2010). It was shown recently that phosphorylation of Red1 is carried out in Cdc28-dependent and Cdc28-independent manners and that Red1 phosphorylation is independent of meiotic DNA recombination (Lai et al., 2011). Cdc28 is the only CDC (cyclin dependent kinase) in *S.cerevisiae* and plays the main role in cell cycle regulation. From G1 to S phase and in S phase Cdc28 is bound to B-type cyclins Clb5,6-Cdc28 and this complex plays a role in entry into the pre-mitotic and pre-meiotic S-phase. But in meiosis, the Clb5,6-Cdc28 complex also has a role in the recombination process. It regulates DSBs formation by phosphorylation of Mer2, a protein that is bound to Spo11 (Henderson et al., 2006). Mre11-Rad50-Xrs2 complex and Sae2 endonuclease are necessary to remove the covalently attached Spo11 from the DNA ends. It was shown that phosphorylation of Sae2 by Cdc28 is required to initiate meiotic DSB resection by allowing Spo11 removal from DSB ends (Manfrini et al., 2010). Cdc28 is required for the processing of DSBs by providing a mechanism for coordinating DSB resection with progression through the meiotic prophase. But localization of Clb5,6-Cdc28 is independent of DSB formation and is rather dependent on meiosis-specific chromosome components such as Red1, Hop1, and a cohesin subunit Rec8. Recently it was found that compromised Cdc28 activity in the meiotic prophase leads to defective SC formation without affecting DSB formation suggesting that CDK-dependent phosphorylation regulates formation of SC (Zhu et al., 2010). Clb5,6-Cdc28 obviously promotes not only the onset of premeiotic DNA replication but also the formation of meiotic DSBs and SC formation.

4.2.4 Ime2 in meiotic recombination

During meiosis, Ime2, a meiosis-specific protein kinase, assumes some function of the Cdc28 complexes. Ime2 is required for critical events in meiosis, including DNA replication (section 3.1.2.). Transition from G_1 to S phase is prohibited by the Clb5,6-Cdc28 inhibitor Sic1 in both mitosis and meiosis. In mitosis, inactivation of Sic1 by phosphorylation is catalyzed by the Cln1,2-Cdc28 complex (Nash et al., 2001), while in meiosis it is catalyzed by Ime2 (Dirick et al., 1995). Ime2 is obviously required for the initiation of DNA replication in meiosis. On the other hand, Ime2 interacts with RPA, a complex required for stabilization of ssDNA during replication and recombination. In meiosis, Ime2 is required for full RPA phosphorylation (Clifford et al., 2005), thus Ime2 affects meiotic recombination processes as well.

4.2.5 Kinases Mec1 and Tel1 in meiotic recombination

Mec1 (hATR) is an essential protein that mediates two important functions: S-phase checkpoint responses (2.1.) and meiotic recombination. Kinases Mec1 and Tel1 phosphorylate the axial element protein Hop1 and promote meiotic recombination using an intact homologous non-sister chromatid rather than a sister chromatid (Carballo et al., 2008). Without this specific phosphorylation, meiotic DSBs are repaired via a Dmc1-independent intersister repair pathway, resulting in diminished interhomolog crossing-over. Phosphorylation of Hop1 by Mec1/Tel1 is required for activation of Mek1, a meiotic paralogue of the DNA-damage effector kinase, Rad53p.

It was proposed that Mec1 and Tel1 also modulate the switch from the open to closed state of telomeres (Dubrana et al., 2001). Telomeres are not elongated every cell cycle. They can switch to an open state for telomerase recruitment.

4.2.6 Mre11 in meiotic recombination

The Mre11-Rad50-Xrs2 complex is required for the initiation of meiotic recombination - for programmed DSBs catalyzed by Spo11 and for break end resection, which is a key step in homologous recombination. It has been proposed that Mre11 assembles on the DSB sites and ensures a link between DSB formation and the processing of break ends (Borde et al., 2004).

4.2.7 Spo11 and Rec8 in meiosis

The Spo11 protein is the catalytic subunit of the meiotic DSB transesterase and is directly responsible for the initiation of meiotic recombination. Rec8 is a meiosis-specific protein required for meiotic sister chromatid cohesion and meiotic recombination. It has been shown that recombination proteins Spo11 and Rec8 also play distinct roles in meiotic DNA replication (Cha et al., 2000). They modulate the progression of meiotic replication: the mutation of *spo11* decreases the length of the S phase, while mutation of *rec8* increases the length of the S phase. It was proposed that meiotic S-phase progression is linked directly to the development of specific chromosomal features required for meiotic interhomolog interactions. During the process of meiotic replication, the future DSB sites are probably marked. The time delay between replication and DSBs may reflect the time required to assemble the proper protein complexes at the target sites.

5. Common problem: DNA unfolding

Organization of DNA sequences into a chromatin structure represents a barrier to processes acting on DNA, like replication and recombination. During these processes chromatin structure has to be remodeled and reestablished after DNA replication and repair. Replication and recombination need access to the sequence in the interior of the double helix DNA and both require DNA topoisomerase to unwind the DNA helix, DNA helicase to open the DNA helix, and ssDNA-binding protein to protect single stranded DNA.

5.1 DNA topoisomerase and DNA helicase

Topoisomerases are enzymes that are able to unwind and wind DNA. They bind to DNA and cut the phosphate backbone of the DNA, the DNA molecule can then untangle, and the untangled DNA is reconnected. Thus, their function in replication, transcription, and recombination is essential. In *S. cerevisiae*, there are three types of topoisomerases: Top1 and Top2 that relax positively and negatively supercoiled DNA, and Top3 that relaxes single-stranded negatively-supercoiled DNA.

Helicases are able to separate strands of the DNA double helix using energy from ATP hydrolysis and are also required for replication, transcription, and recombination. Helicases Sgs1, Srs2, Rrm3, Dna2, and Rad3 form a complex interacting network with other DNA replication and recombination proteins to preserve genomic integrity. Sgs1 and Srs2 are involved in genome integrity maintenance and meiotic recombination; Rrm3 is involved in telomere and rDNA replication, and Ty1 transposition; nuclease and helicase Dna2 is required for Okazaki fragment processing and DNA repair; Rad3 is involved in nucleotide excision repair and transcription (SGD; http://www.yeastgenome.org/).

Sgs1 is a helicase of the RecQ family, similar to human BLM and WRN proteins that are implicated in Bloom and Werner syndromes. Sgs1 interacts with many proteins and has

very complex function, which is a good example of the cooperation between replication and recombination.

- Sgs1 and Srs2 helicases control distinct pathways of HR during DNA replication and the restart of stalled replication forks. Recombination-dependent cruciform structures are formed on damaged chromatids and Sgs1 and Srs2 counteract their formation (Liberi et al., 2005). It was shown that the double mutation *sgs1srs2* leads to a synthetic growth defect and that a mutation in *rad51* fully rescues the *sgs1 srs2* synthetic defect (Gangloff et al., 2000). It was therefore concluded that defects in *sgs1 srs2* mutants are caused by misregulated HR during DNA replication.
  During regulation of HR, Sgs1 functions in a complex with Top3 and Rmi1, a DNA-binding protein with a preference for cruciform structures (Mullen et al., 2005). The Sgs1-Top3-Rmi1 complex is crucial for resolution of recombination intermediates such as Holliday junctions. The complex interacts with recombination protein Rad51. It was shown that Rad51 helps recruit Sgs1-Top3 to sites of replicative damage (Shor et al., 2002).
- During meiosis Sgs1 negatively regulates not all HR mechanisms, but specifically crossovers (Rockmill et al., 2003). The mutation *sgs1* leads to an increase in closely spaced crossovers without an increase in non-crossover products (Oh et al., 2007). The anti-crossover activity of Sgs1 is opposed by the pro-crossover activities of the ZMM proteins. Srs2 play a similar role as Sgs1. Double mutants *sgs1srs2* increase crossovers and overexpression of SRS2 nearly eliminates crossovers (Ira et al., 2003). Sgs1 and Srs2 obviously regulate the processing of recombination intermediates during DNA replication and promote non-crossover products.
  Sgs1 also functions in a Sgs1-Top3-Rmi1 complex during meiosis. Mutants *spo11* that have no recombination between homologous chromosomes, still form viable spores if there is also a *top3* mutation (Gangloff et al., 1999). This result indicates that Top3 is required to complete recombination successfully.
- Sgs1 has a direct role in the DNA damage response during mitotic DNA replication. Sgs1 is one of the components of the S-phase checkpoint response, which senses DNA damage or a blocked fork progression during DNA replication (Frei & Gasser, 2000). Sgs1 associates with signal-transducing kinase Rad53 in S-phase-specific foci.
- Sgs1 interacts with the Top2 topoisomerase, which is the major mitotic post-replication decatenase. In *top2* mutants, chromosomes segregate improperly, leading to chromosome loss and disomy. Because Sgs1 acts along the same pathway as Top2, it has been suggested that Sgs1-Top2 is important for the decatenation of sister chromosomes (Watt et al., 1995). In meiosis, the Sgs1-Top2 complex has the similar role.

5.2 ssDNA-binding protein

Replication protein A (RPA) binds strongly and in long clusters to ssDNA and form a nucleoprotein filament. Because of its protective function on ssDNA ends, RPA has a central role in DNA repair, meiotic recombination, and also in replication checkpoints.

RPA recruits checkpoint kinase Mec1 (hATR) to ssDNA. Such activated Mec1 further phosphorylates its substrates during the DNA damage checkpoint response. It has been proposed that RPA is needed to determine the severity of DNA damage and also to initiate a full checkpoint response (Pellicioli et al., 2001). DNA damage and the extent of ssDNA are probably monitored by the binding of the RPA to ssDNA (Lee et al., 1998).

6. Post-translational modifications

Post-translational modifications, with their key role in controlling protein function, play an important role in the maintenance of genome integrity. Sumoylation, phosphorylation, and ubiquitination are especially important for the operation of replication and recombination proteins in order for them to execute their functions in a rapid and efficient manner. While ubiquitination leads in most cases to proteasomal degradation of the target protein, there are also many non-proteolytic functions of ubiquitin (Ulrich & Walden, 2010). Monoubiquitylation is not directed at proteolysis; it often reveals a new binding domain. Polyubiquitin chains that are linked through distinct Lys residues of ubiquitin also have functions that are independent of proteolysis; they might activate kinases or provide protein interaction changes (Hicke et al., 2005). Non-proteolytic functions of monoubiquitylation and polyubiquitylation are particularly important in the control of the DNA damage response and DNA repair pathways. The small ubiquitin-like modifier (SUMO), which modifies proteins by regulation of their protein-protein interactions, allows the assembly and disassembly of protein complexes to be modulated. Sumoylation and ubiquitination both occur as the result of sequential action of specific enzymes: activating enzyme (E1), conjugating enzyme (E2), and ligase (E3). SUMO and ubiquitin are covalently attached to the target protein; sometimes it is the same lysine residue of a target protein that can be alternatively modified by either SUMO or ubiquitin. Phosphorylation, the addition of a phosphate group (PO4) to a target protein, results in a conformational change in the protein and consequently leads to its altered activity. Reversible phosphorylation is catalysed by kinases (phosphorylation) and phosphatases (dephosphorylation). Beside its central post-translational role, phosphorylation is also a regulator of the SUMO pathway (Hietakangas et al., 2006).

Here are some examples of post-translational modifications of replication and recombination factors:

- RecQ helicase Sgs1 is specifically sumoylated under the stress of DNA double strand breaks (Lu et al., 2010). SUMO together with the Sgs1-Top3 complex counteracts the accumulation of crucial intermediates at replication forks during replication resumption processes (Branzei et al., 2006). Sumoylation of Sgs1 at K621 is uniquely required for its role in telomere–telomere recombination for Type II cells.
- Repair proteins yKu70, Smc5, and Smc6 are modified by SUMO (Zhao & Blobel, 2005). Smc5 is sumoylated by Mms21 SUMO ligase in response to DNA damage and forms a complex with Smc6 that has a role in DNA repair and segregation of repetitive chromosome regions (Cost & Cozzarelli, 2006).
- In the NHEJ pathway the Nej1 protein recruits anti-recombinogenic helicase Srs2 to DSB repressing HR and favoring NHEJ or SSA. Interaction between Nej1 and Srs2 is enhanced by phosphorylation of Nej1 (Carter et al., 2009).
- Phosphorylation of Sae2, a nuclease that regulates DNA end resection in mitotic and meiotic cells, determines whether a DSB is channelled into NHEJ or HR (Huertas et al., 2008).
- Nuclease Exo1 that generates ssDNA is regulated by phosphorylation. Rad53-dependent phosphorylation reduces Exo1 activity (Morin et al., 2008).
- Rad51 has a central role in HR. Human Rad51 is phosphorylated in response to HU. Its phosphorylation has an activating role (Sorensen et al., 2005).
- Rad52 is sumoylated after DNA damage and during meiosis and this sumoylation is essential for activating HR and SSA (Sacher et al., 2006). Rad52 is excluded from the

nucleolus containing rDNA repeats to diminish the negative effect of HR in repetitive sequences. Cells with mutated Rad52, which cannot interact with SUMO, form foci within the nucleolus, resulting in slightly elevated rDNA recombination (Torres-Rosell et al., 2007).

- Several components of the replication fork including Mrc1 are phosphorylated after fork stalling, including Mrc1, which plays roles in both the S phase checkpoint and at the replication fork. Phosphorylation of Mrc1 is required for activation of the Rad53 kinase during the S phase checkpoint but is not required for DNA replication (Lou et al., 2008).
- Phosphorylation of histone H3 has a role in DNA replication. Phosphorylation of H3 Thr45 is mediated by the kinase Cdc7–Dbf4. It has been shown that Thr45 phosphorylation peaks during DNA replication and that the loss of this phosphorylation site causes phenotypes consistent with replicative defects (Baker et al., 2010).
- Topoisomerase Top2 cleavage and re-sealing of the phosphodiester backbone is required for replication and recombination processes. It has been shown that sumoylation is essential for Top2 functioning (Bachant et al., 2002).
- Kinetochore proteins Ndc10, Bir1, Ndc80, Cep3 were also shown to be sumoylated (Montpetit et al., 2006).

Of particular interest are the post-translational modifications of proteins like PCNA that directly connect replication and recombination processes. Sumoylation and different types of ubiquitination on PCNA activate a different set of functions to deal with particular types of replication stresses:

- PCNA is essential in DNA replication and DNA repair. It is loaded on chromatids and functions as a processivity factor for DNA polymerases and other proteins that regulate replication-associated processes. Sumoylation and ubiquitination of PCNA both occur in the S phase: sumoylation during normal S-phase and ubiquitination following DNA damage. Sumoylation of PCNA prevents unwanted recombination repair during DNA replication. PCNA sumoylation favors physical interactions with anti-recombinogenic helicase Srs2 and replication forks (Papouli et al., 2005; Pfander et al., 2005). Helicase Srs2 inhibits recombination by disrupting Rad1 nucleoprotein filaments from ssDNA (Veaute et al., 2003). DNA damage induces mono- or poli-ubiquitination of PCNA. Monoubiquitination of PCNA favors interaction with translesion DNA polymerases and promotes error-prone translesion synthesis, while polyubiquitination on the same residue promotes error-free damage repair, which relies on recombination mechanisms (Hoege et al., 2002). Poliubiquitination with recombination repair is favored over monoubiquitination.

7. Telomere: DNA replication can be replaced by recombination

Telomeres are nucleoprotein structures at the ends of eukaryotic chromosomes. They play a crucial role in maintaining genomic stability by providing chromosome-end protection. Telomeric DNA with repetitive guanine-rich DNA sequences is able to form protective t-loop and G-quartet structures; and together with interacting specific proteins, form a protective 'cap' that distinguish telomeres from DNA double-strand breaks (Simonsson, 2001).

Telomeres are duplicated by special DNA replication using a specific DNA polymerase, telomerase. When this special telomere replication is unavailable, DNA recombination at telomeres can be replaced by recombination mechanisms.

7.1 Telomere DNA replication

Because of single-stranded 3′ overhangs and bound proteins, telomeres are specifically replicated by telomerase. Telomerase is a DNA polymerase that is specifically dedicated to the replication of chromosome ends. It is composed of several components: a reverse transcriptase catalytic subunit - RNA that provides a template for DNA synthesis, an Est2 catalytic subunit, and additional associated proteins, Est1 and Est3. Cdc13 ssDNA telomere binding protein is a key factor in telomerase recruitment. The telomere binding Ku heterodimer (Ku70,80) with its role in the maintenance of telomere DNA structure also plays a positive role in the Cdc13p-dependent recruitment of telomerase. It also stimulates telomerase activity after telomerase is bound to the telomere. The telomere binding protein Rap1 is involved in telomere length regulation and telomeric silencing; Rap1p in complex with Rif1 and Rif2 forms a higher-order structures that is part of a system for telomere length measurement (Ji et al., 2008).

Telomerase activity has been detected throughout the entire cell cycle, but telomere elongation is restricted to late S phase when replication machinery is available. It has been shown that telomere elongation is coincident with normal DNA replication; telomerase action is tightly co-regulated with conventional replication (Diede & Gottschling, 1999).

As regards replication of sub-telomeric regions, there are no converging forks that would complete replication when forks collapse. In sub-telomeric regions, DNA repair mechanisms are absolutely required to restart the collapsed fork.

7.2 Telomere maintenance by recombination

Without telomerase, telomeres shorten with replication and signal cell senescence. The final consequence of telomere erosion is the loss of capping proteins, which leaves telomeres exposed to DNA repair mechanisms, potentially inappropriate recombination events or end-to-end fusion (Blackburn, 2000). However, rare survivors bypass senescence and death. Homologous recombination (HR) could slow senescence and support the growth of the rare survivors. HR is suppressed where telomere sequences are of normal length; however, telomere recombination is allowed when telomeres erode in the absence of telomerase activity or incomplete replication. Most human malignant cells become immortalized by telomere extension due to the activation of telomerase, while about 10% of human cancers activate a recombination-mediated elongation, the so-called alternative lengthening of telomeres (ALT). Recombination mechanisms in budding yeast that enable telomere elongation in the absence of telomerase are analogous to ALT (Lydeard et al., 2007). There are two types of survivors when telomerase is absent and both depend on the Rad52 recombination protein (Chen et al., 2001). Type I cells exhibit the amplification of Y′ sequences and have very short telomere repeats on the chromosome ends. They depend on Rad51, Rad54, Rad55, Rad57 proteins, like DSB repair by HR. Type I cells show accelerated loss of viability. Type II cells exhibit extremely elongated and heterogeneous telomere repeats and only modest Y' amplification. They depend on Rad50, Mre11, and Xrs2 proteins, like DSB repair by SSA. Type II cells show a slower rate of senescence. It was shown that Type II cells with long telomere repeats and dependence on Rad50, resemble human ALT

cells (Dunham et al., 2000). Type II cells are as efficient as wild type in maintaining cell survival. Telomere recombination is as efficient as telomerase, but cells using recombination for telomere maintenance instead of replication by telomerase had a shortened replicative life span or accelerated cellular aging (Chen et al., 2009b). In the absence of telomerase and both recombination pathways, cells fail to produce survivors.

It has been shown that short telomere is the preferred substrate of telomerase and is also sufficient to recruit recombination proteins; on the other hand, ssDNA at telomeres does not appear to be sufficient to attract recombination proteins (Pennaneach et al., 2006). The Rad52- Cdc13 focus is found to colocalize with short telomeres in 50% of cells. It has been proposed that a burst of resection at a single telomere marks the transition between recombination-resistant and recombination-prone states at telomeres.

Telomeres bind numerous DNA repair and damage checkpoint proteins as DSBs, but they activate neither DNA repair nor DNA damage checkpoint pathways. Paradoxically DNA repair and checkpoint proteins do still play critical roles in telomere stability (Lydall, 2003).

8. Ecm11, yeast protein with a role in replication and recombination

Ecm11 is a protein of the budding yeast *S.cerevisiae.* The predicted *ECM11* gene product has 302 amino acids and shows no significant similarity to any other protein in the databases. From the microarray hybridization data available in the Stanford Genome Database (SGD; http://www.yeastgenome.org/), it is apparent that the *ECM11* transcript does not oscillate during the cell cycle, but is significantly elevated during meiosis. It was confirmed that the level of protein Ecm11 is in accordance with the mRNA: the level of Ecm11 protein is low in mitosis, but high in meiosis (Zavec et al., 2008). The highest level of Ecm11 is in the early-middle phase of sporulation. The central, unique features of meiosis are homologue pairing, interhomologue recombination, and synaptonemal complex formation. These regulated events are expected to use meiosis-specific regulators and this was the supposed role of Ecm11. In our previous work we have demonstrated that Ecm11 is indeed required in meiosis (Zavec et al., 2004). Mutants *ecm11Δ* exhibit complex defects in meiotic replication and recombination: diminished meiotic DNA synthesis, reduced crossing over, increased gene conversion events and reduced levels of sporulation and spore viability (Fig. 2).

8.1 Ecm11 has important role in meiotic recombination

ECM11 showed an early to middle pattern of induction in meiosis. There are three groups of meiotic genes with the nearly identical expression pattern as *ECM11*: the meiotic recombination genes such as *MND1* and *REC114*, the synaptonemal complex genes such as *RED1* and *MSH4*, and the meiotic specific cohesion gene *REC8* (SGD; http://www.yeastgenome.org/). Such an expression pattern of *ECM11* indicates that Ecm11 could have a role in meiotic recombination process. It has been shown that *ecm11* homozygous diploid strains sporulate more slowly and less efficiently than wild type strains and that the viability of spores was reduced to 50% (Zavec et al., 2004). Using recombination tests, it was shown that *ECM11* is required for crossing over, but not for gene conversion.

8.1.1 The *ecm11* mutation affects sporulation efficiency

In the homozygous *ecm11* mutants, a delay in sporulation was observed and there was about a 30% reduction in the maximal level of asci obtained, compared to the isogenic wild

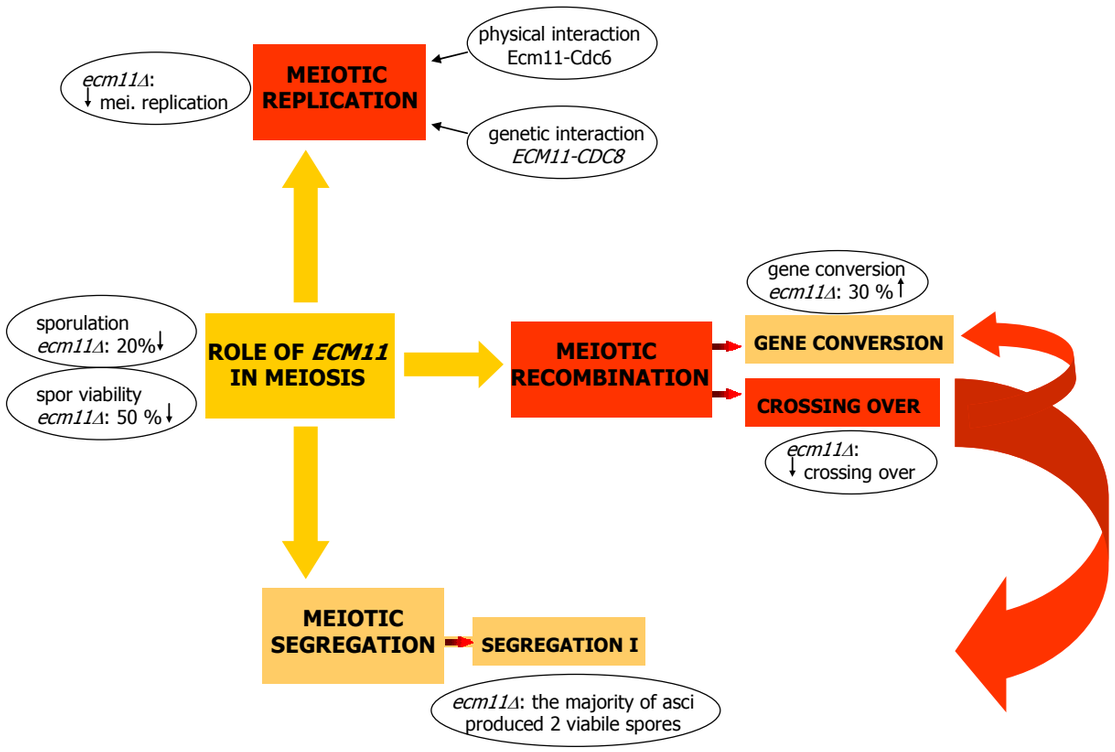

Fig. 2. The role of yeast protein Ecm11: mutants *ecm11Δ* exhibit complex defects in meiotic replication and recombination: diminished meiotic DNA synthesis, reduced crossing over, increased gene conversion events and reduced levels of sporulation and spore viability.

type strain. Heterozygous strains yielded slightly higher sporulation efficiency *ecm11* mutants. Wild type strains carrying additional *ECM11* on the centromeric plasmid also showed reduced sporulation efficiency comparing to wild types. Obviously, sporulation efficiency depends on the copy number of Ecm11 protein in the cell during meiosis. Since more Ecm11 than usual in the cell leads to lower sporulation efficiency, Ecm11 is probably a part of a heterologous protein complex that requires the correct balance among these proteins.

The kinetics of the sporulation process shows that spores appeared about four hours later in *ecm11* mutants than in wild type. Both strains complete sporulation at the same time, but *ecm11* strains produce lowers level of asci. Since deletion of *ECM11* resulted in reduced meiotic process progression with reduced maximal level of asci, Ecm11 was defined as a positive effector of meiosis.

8.1.2 Ecm11 is required for crossing over, but not for gene conversion

Asci of the parental MAS and homozygous *ecm11* mutants were dissected and compared. In the parental strain, 98% of spores germinated after dissection, while only 50% spores of the *ecm11* mutants survived. Beside strongly reduced spore viability in the *ecm11* mutants, a strongly elevated fraction of tetrads exhibiting two viable spores in *ecm11* mutants was observed (Zavec et al., 2004). The majority of *ecm11* asci (56%) produced only two viable spores, while only 1% of such asci were observed in the parental strain. This result shows non-disjunction of homologous chromosomes at the first meiotic division.

Crossing over frequency was measured in two-viable-spores asci in the *ecm11* strain. In 84% of asci both surviving spores had the same URA phenotype, indicating that both functional spores inherited sister chromatids. Obviously, *ECM11* is required for crossing over. Additionally, since in meiosis I homologous chromatids are separated, the effect of Ecm11 in fidelity of chromosome segregation can be confined to meiosis I. Surprisingly, the results of the return-to-growth experiment showed slightly increased gene conversion events in *ecm11* mutants. This result raises the possibility that *ecm11* mutation impairs the crossover process at an early step of recombination, at the differentiation of intermediates into crossovers or non-crossovers.

The *ECM11* gene is required to produce a normal level of crossover, but not noncrossover events, just like genes required for synaptonemal complex formation (*ZIP1, ZIP2, ZIP3*), mutS homologues (*MSH4, MSH5*), some mismatch repair genes (*MLH1, MLH3*, *EXO1*) and meoisis specific DNA helicase *MER3* (Borner et al., 2004). So, Ecm11 must belong to the specific set of proteins that are required for crossing over. Mutants of some of those genes (*msh5, mer3, zip1, zip2, zip3*) exhibit normal levels of double-strand breaks and noncrossover products but strong coordinate defects in single-end invasions, double Holliday junctions and crossover products, thus implying that those mutants are specifically defective in the formation and functioning of single-end invasions (Borner et al., 2004).

As proper segregation of homologous chromosomes during the reductional division of meiosis does not require gene conversion, but does require crossing over to establish chiasmata, which physically connect homologues after disassembly of the synaptonemal complex, inappropriate segregation of chromosomes in *ecm11* mutants could be due to reduced crossing over in those cells.

8.2 *ECM11* is required for meiotic DNA replication

To determine if deletion of *ECM11* influences meiotic replication, the DNA content of yeast cells was analysed by flow cytometry. FACS analysis show that the fraction of *ecm11* mutants entering S phase is reduced compared to the wild type. The *ecm11* mutants enter S phase at the same time as wild type cells, but it is less efficient in the knockout strain. The replication process was the most intense between the second and the fourth hour of sporulation. In this period, the percentage of 4N cells in the wild type cell population increased by 36%, while in the mutant cells this increase was only 18%. The hindrance of DNA replication caused by the deletion of the *ECM11* gene may be due to many reasons: the lower efficiency of origin firing, the lower progression of DNA replication or as a consequence of modifications in some other meiotic process. Based on our FACS data we cannot exclude any of these possibilities. Since, in all strains tested, deletion of the *ECM11* gene has no impact on generation time during vegetative growth, we assume that the effect of the *ecm11* mutation on S phase is limited to meiosis.

In the two-hybrid screen it was found that Ecm11 strongly interacts with an essential protein Cdc6, which has a pivotal role in the initiation of DNA replication (Zavec et al., 2000). Genetic interactions between Cdc6 and Ecm11 were also observed. Moderate suppression of the *cdc6-1* mutation by overexpression of *ECM11* was detected (Zavec et al., 2000) and deletion of *ECM11* in *cdc6-1* genetic background enhances thermosensitivity of the *cdc6-1* mutation (unpublished result). In addition, *ECM11* shows synthetic lethality with *CDC8*, a gene coding thymidylate kinase, which is required for DNA synthesis (Tong et al., 2004). These data suggest the direct involvment of *ECM11* in DNA replication.

In meiosis, Cdc6 is required for premeiotic DNA replication as in the vegetative cell cycle, but the origin-bound Cdc6 is protected from degradation and occupies origins throughout the meiotic cycle (Ofir et al., 2004). Origin-bound Cdc6 could reflect a change in chromatin structure that occurs in meiosis and Ecm11 bound to Cdc6 could be a part of these changes.

8.3 Ecm11 is modified by SUMO during meiosis

8.3.1 Sumoylation status of Ecm11 during meiosis

In a wide search of protein-protein interactions it was found that Ecm11 interacts with SUMO (Smt3) in the two-hybrid system (Ito et al., 2001; Yu et al., 2008). The Ecm11 protein has two lysine residues, K5 and K101, with a corresponding surrounding sequence IKTE that could accept SUMO. It was confirmed by immunoprecipitation that Ecm11 is sumoylated during meiosis and that Ecm11 interacts with SUMO covalently (Zavec et al., 2008). The majority of Ecm11 protein in the cell is sumoylated during meiosis. The HA antibodies recognized the HA-tagged Ecm11, as well as additional ~10 and ~20 kDa larger species, which correspond to the molecular mass of one or two copies of mature SUMO. Sumoylation of Ecm11 was confirmed by anti-Smt3 reactivity on anti-HA immunoprecipitated samples. Multiple sumoylation was already observed for other sumoylated proteins, e.g. Rpb1, the largest subunit of RNA polymerase II (Pol II) (Chen et al., 2009a).

8.3.2 Sumoylation of Ecm11 is essential for Ecm11 functioning in meiosis

The importance of Ecm11 sumoylation for progression through meiosis was investigated by studying the effect of mutations of predicted SUMO consensus sites in Ecm11 on sporulation efficiency (Zavec et al., 2008). Lysines K5 and K101 in the predicted SUMO consensus sites were mutated to the uncharged amino acid asparagine. Mutation of the predicted sumoylation site K5 affects the biological function of Ecm11 in meiosis. Mutation of K5 led to a reduction of sporulation to the same level as that seen in the mutant with the deleted *ECM11* gene, while mutation of K101 did not affect sporulation level. These results suggest, firstly, that the Lys5 at N-terminus of Ecm11 is modified by SUMO during meiosis and, secondly, that sumoylation is essential for the biological role of Ecm11 in meiosis and directly regulates Ecm11 function in meiosis.

8.3.3 Ecm11 is probably modified by phosphorylation

As described previous (section 5.), beside sumoylation, phosphorylation is the most important modification for replication and recombination proteins. Most components of SCs including Zip1, Hop1, Red1, Mre4, and Rec8 are phosphoproteins, but the functional significance of this phosphorylation and the kinase responsible for the phosphorylation remains to be characterized (Zhu et al., 2010). Ecm11 also contains many predicted phosphorylation sites.

9. Conclusion

In this chapter connections between replication and recombination processes are presented. Studying of proteins that affect both processes will further clarify the relationship between these two processes. One of such proteins is yeast protein Ecm11, which affects meiotic replication and crossing over and is typically modified by sumoylation. Studying such

proteins and discussing the relationship between replication and recombination from different points of view may improve understanding of living systems on a higher level.

10. References

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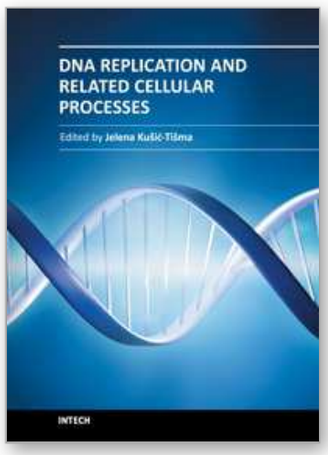

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Since the discovery of the DNA structure researchers have been highly interested in the molecular basis of genome inheritance. This book covers a wide range of aspects and issues related to the field of DNA replication. The association between genome replication, repair and recombination is also addressed, as well as summaries of recent work of the replication cycles of prokaryotic and eukaryotic viruses. The reader will gain an overview of our current understanding of DNA replication and related cellular processes, and useful resources for further reading.

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