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The Pathways of Double-Strand Break Repair

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1. Introduction

1.1 Induction and repair of double-strand breaks (DSBs) in the DNA

DNA encodes and transmits genetic information into the progeny of cells and organisms. As a result, processes associated with DNA replication, repair and recombination are at the center of biological research. Although the double-stranded nature of the DNA molecule is not a requirement for its replication or transcription, it is essential for the repair of practically all forms of damage that are limited to one DNA strand. Thus, in the base excision repair (BER) pathway, the damaged base is excised by the appropriate DNA glycosylase and the resulting apurinic/apyrimidinic site is recognized by the AP-endonuclease (APE1) which opens the sugar phosphate backbone and removes the sugar residue (Fig. 1A). The resulting single nucleotide gap is filled-in using information from the complementary strand with the help of DNA polymerase β (polβ) and the sugar phosphate backbone is resealed with the help of XRCC1/DNA LigaseIII (LigIII) complex (Sancar et al., 2004). In an alternative form of this repair pathway, more nucleotides are removed from the vicinity of the damaged base and are subsequently replaced by the DNA polymerase, hence the name long-patch base excision repair.

A further example of a repair pathway relying exclusively on the complementarity of the DNA strands for the faithful restoration of the DNA molecule is the nucleotide excision repair pathway (NER) (Fig. 1B). In this repair pathway gross structural distortions are recognized in the DNA rather than altered bases. Such structural alterations can be generated by pyrimidine dimers forming after exposure to UV light, as well as by several other forms of DNA lesions, including DNA crosslinks and DNA "bulky" adducts. Upon their recognition by a multi-protein complex (see Fig. 1B for details) and with the help of two independently acting 3'- and 5'- excision nucleases XPG and XPF/ERCC1 respectively, an incision is placed 6 ±3 and 20 ±5 nucleotides upstream and downstream of the pyrimidine dimer ultimately removing an approximately 24-32 nt single stranded DNA segment including the lesion. The resulting gap is filled in, again using information available on the complementary strand with the help of a polymerase. The continuity of the DNA is finally restored by ligation with DNA Ligase I (LigI) (Sancar et al., 2004).

This fundamental concept of DNA repair, i.e. the use of a complementary strand to restore sequence information in the damaged strand, fails when complex damage is generated in the DNA consisting of multiple lesions distributed on both strands of the DNA in close proximity (Fig. 1C). Such forms of DNA damage are generated after exposure of cells to

ionizing radiation (IR) and are the direct consequence of the energy deposition patterns of this physical cytotoxic agent (Fig. 1C). The most widely investigated, complex form of damage is the DNA double-strand break (DSB). DSBs are highly dangerous DNA lesions that have been implicated not only in cell death but also in the induction of mutations and in carcinogenesis.

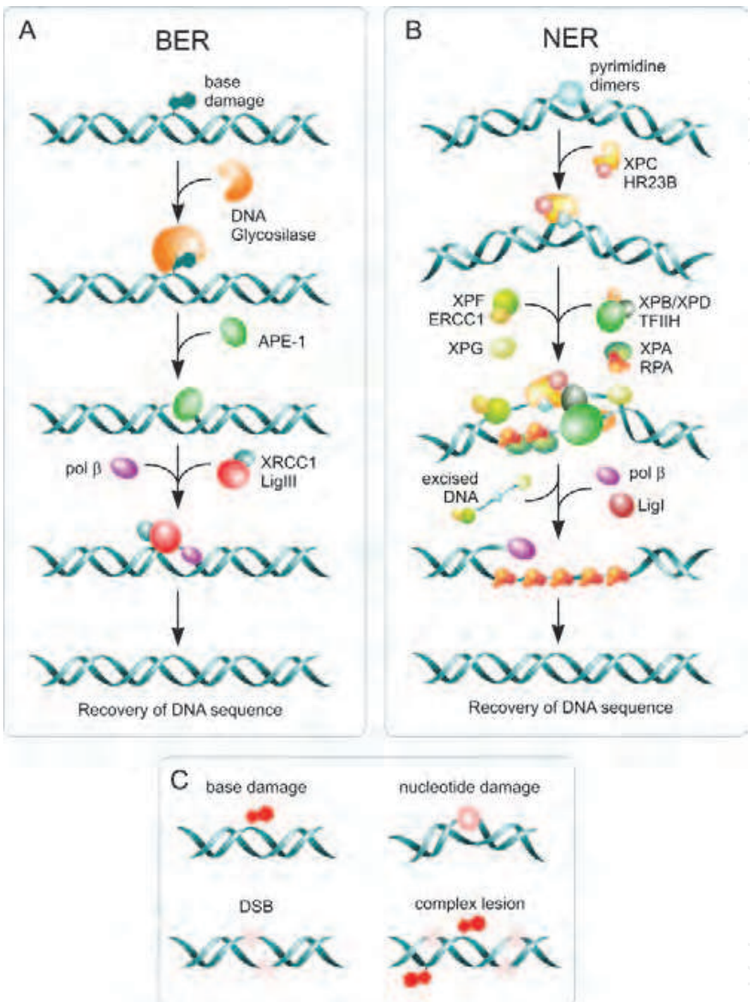


Fig. 1. Base excision repair (BER) and nucleotide excision repair (NER) pathways. Both BER and NER repair pathways utilize the complementary DNA strand to restore sequence information lost in the damaged DNA strand. A) Schematic representation of the basic steps followed during short-patch BER (see text for details). B) Main sequence of events and enzymatic activities implicated in NER. C) Forms of lesions generated in the DNA by IR.

The difficulties that cell faces in its attempt to faithfully process DSBs have two distinct aspects. First, the resulting disruption of the DNA molecule (note that disruption of the DNA molecule does not occur in case of lesions processed by BER or NER) physically interrupts its continuity and destabilizes the surrounding chromatin. Second, since both DNA strands carry damage closely juxtaposed, an intact template is lacking for ensuring the faithful restoration of the sequence in the vicinity of the break. The selective pressure for

evolving mechanisms for the detection and processing of DSBs would have been low had this type of lesion been extremely rare. However, in addition of IR, a number of chemical and physical cytotoxic agents generate DSBs. Most importantly, however, DSBs are also generated during the normal life cycle of the cell, particularly during DNA replication or in meiosis (Baudat & de Massy, 2007; Longhese et al., 2009), as well as during V(D)J and class switch recombination required for the differentiation of B and T cells of the hematopoietic system (Franco et al., 2006; Maizels, 2005). To cope with these multiple sources of DSBs, cells have evolved sophisticated mechanisms for detecting and repairing this form of DNA lesion. Notably, these repair mechanisms have been intimately coupled to the cell cycle, transcription and apoptosis machineries, suggesting a close coordination with the overall cellular metabolism.

Two conceptually different mechanisms can in principle remove DSBs from the genome in cells of higher eukaryotes. Homologous recombination repair (HRR) is equipped to maintain fidelity in the sequence of the DNA molecule, but because the damage affects both DNA strands it retrieves information from a homologous DNA molecule that is used as a template. There are two sources of homology in mammalian cells. The homologous chromosome that is present throughout the life cycle of the cell and the sister chromatid that is generated after DNA replication and which therefore exists only during the S and G2 phases of the cell cycle. Existing evidence supports the view that HRR requires the sister chromatid as a source of template, a requirement that automatically restricts the function of this repair pathway to the S and G2 phases of the cell cycle. This requirement probably derives from the fact that in a eukaryotic cell nucleus the homologous chromosomes are accommodated in distinct and frequently distantly located domains that renders search for homology (a key step of HRR, see below) difficult, if not impossible (Cremer & Cremer, 2001; Folle, 2008).

Non-homologous end joining (NHEJ), on the other hand, simply restores integrity in the DNA by joining the two ends without necessarily preserving the original sequence. As a result, it is error prone. Because a second DNA molecule is not required for the function of this repair pathway, it remains active throughout the cell cycle, but has a limited contribution to the rejoining of DNA lesions generating a single DNA terminus.

The fact that at least two genetically and conceptually distinct repair pathways are involved in the elimination of DSBs, poses questions regarding their coordination. If these pathways operate independently of each other it is possible that they compete against each other. If they collaborate, the question arises as to how their functions are coordinated. In this regard, it appears puzzling that cells of higher eukaryotes appear programmed to utilize preferentially NHEJ.

In the following sections we summarize the salient features of HRR and NHEJ and explain the concepts underlying their operation. Further, we describe a "dormant" pathway of DSB repair that unfolds its activity mostly when D-NHEJ for some reason fails and which therefore is considered to have a backup nature. Finally, we cover connections between DSB repair and cell cycle progression and discuss potential sources of errors during DSB repair that affect genomic stability and may lead to cancer development.

2. Homologous recombination repair – the only genuine repair process

DSB repair based on homology is frequently termed homologous recombination repair (HRR). A breakthrough in our understanding of the process of homologous recombination

(HR) in general and of HRR in particular was the model proposed in 1964 by Robin Holliday to explain meiotic recombination. The model introduced several key concepts including a mechanism for the exchange of genetic material between homologous chromosomes through the formation of what is now known as Holliday junction (HJ) (Liu & West, 2004) (see below for description). The Holliday model described some of the basic steps of the recombination process, but was unable to explain all sets of available genetic data. This was later achieved by a model proposed by Jack Szostak, now known as the double-strand break repair model (DSBR) (Szostak et al., 1983). Furthermore, analysis of genetic experiments in Drosophila revealed that DNA recombination may not require the formation of a Holliday junction and may instead depend on what is now known as synthesis-dependent strand annealing (SDSA) (Ferguson & Holloman, 1996; San Filippo et al., 2008). Recombination events carried out by this mechanism in mitotic cells lack crossover products (exchange of chromosome arms).

All current recombination models are formulated on the basis of genetic data and emphasize the role of HR during meiosis or mitosis. The meiotic function of HR mediates the exchanges of genetic material between the homologous chromosomes of the gamete precursor cells and ensures genetic diversity in the progeny (San Filippo et al., 2008).

Genetic and biochemical data provide strong evidence for the involvement of mitotic HR in the repair of DSBs. Moreover, HR is required for the restart of blocked or collapsed replication forks, as well as during the repair of inter-strand crosslinks (ICLs) (Ide et al., 2008; Nikolova et al., 2010; Petermann et al., 2010). The ultimate goal of HRR is to assist a DNA molecule that has suffered sequence information loss as a result of damage to both strands, to retrieve this information from an undamaged homologous DNA sequence. To this end, damaged and undamaged DNA molecules will need to directly interact, i.e. to undergo synapsis. In particular, the damaged DNA molecule will need processing to generate DNA forms capable of "reading-off" sequence information. Also the chromatin structure on both molecules will need to be modified to facilitate the search for homologous regions in neighboring DNA molecules. Once homology has been found sequence information will need to be copied by appropriately directed DNA synthesis, and finally the synapsed molecules will need to be separated.

Because DSBs are frequently generated in the genome accidently, the cell needs to be prepared for their repair by maintaining sufficient pools of repair factors. Indeed, there is evidence that in eukaryotic cells the level of the repair proteins is higher compared to the level of other proteins of the cellular metabolism (Shrivastav et al., 2008). These pools may have a cell cycle component for repair pathways such as HRR that show preferential function in certain phases of the cell cycle.

In addition to the random induction of DSBs after accidental or intentional exposure to physical or chemical agents, cells also induce DSBs in their genome in a programmed fashion as part of certain differentiation programs. The differentiation of germ cells and of the cells of the hematopoietic system is a good example along these lines. Programmed DSBs for such functions are generated through the action of specific enzymes (Spo11 during meiosis and Rag1/Rag2 during V(D)J recombination). In general, these DSB inducing nucleases interact with components of the repair pathways that are associated with the proper recognition and processing of the generated DSBs (Keeney et al., 1997; McBlane et al., 1995; Oettinger, 1992). Although there is evidence that HR events may be initiated by a single-strand break (Metzger et al., 2011), it is widely accepted that the ultimate initiating event of homologous recombination is the DSB. This recognition implicates the DSBR and

SDSA repair models in the mechanistic foundation of DSB repair through homologous recombination (Brugmans et al., 2007; Pardo et al., 2009; Wyman & Kanaar, 2006).

To accommodate the specific requirements of DSB repair as mediated by DNA homology, HRR starts with the resection of DNA ends around the DSB, causing the formation of 3′-single stranded DNA (ssDNA) regions (West, 2003; Wyman & Kanaar, 2006). This form of DNA can invade and pair to homologous sequences present in an intact molecule and be directly extended by polymerization to copy missing sequence information (see below). Therefore, the effectiveness of HRR may be dictated by the ability of cells to execute end resection in a proper orientation, immediately after the generation of the DSB. In cells of higher eukaryotes the initial DNA end processing is orchestrated by the Mre11/Rad50/Nbs1 (MRN complex) (Fig. 2) (D'Amours & Jackson, 2002; Rupnik et al., 2010), assisted by the functions of recently identified resection promoting factor CtIP (Fig. 3) (Farah et al., 2009; Sartori et al., 2007). The MRN complex exhibits multiple activities many of which are implicated in HRR. Surprisingly, despite its nuclease activity, many reports pointed out that MRN may not be directly involved in the extensive resection of DNA ends to generate the 3′ ssDNA, suggesting that other enzymes with nuclease functions should fulfill this requirement (Longhese et al., 2010; Mimitou & Symington, 2009; Stewart et al., 2010). Thus MRN may have a regulatory role in the coordination between different DSB repair pathways (Borde & Cobb, 2009; Rupnik et al., 2010; Stracker & Petrini, 2011).

The MRN complex is one of the first proteins recruited to DSBs. It consists of the Mre11 nuclease, the Rad50 protein, an ATP-binding polypeptide with bridging functions through a coiled-coil motif and the Nbs1 protein, a polypeptide rich in protein-protein interaction domains (Fig. 2) (Stracker & Petrini, 2011).

The significance of the MRN complex in DSB repair and meiotic recombination was first shown in yeasts by genetic screening of mutants hypersensitive to DNA damaging agents (D'Amours & Jackson, 2002). After the cloning of the yeast *MRE11* and *RAD50* genes, homologues were identified in all model organisms (Ajimura et al., 1993; Chin & Villeneuve, 2001; Dolganov et al., 1996). In addition, it was shown that in higher eukaryotes dysfunction of *MRE11* underlies the ataxia-telangiectasia-like disorder (ATLD), implicating thus Mre11 in ATM dependent DSB repair and signaling pathways (Stewart et al., 1999). However, the identification of the human Xrs2 homolog (the third subunits of the yeast MRX complex) was hampered owing to its high sequence diversity between species.

Ultimately, it was shown that the gene mutated in the Nijmegen breakage syndrome, *NBS1,* is the human *XRS2* homolog, and that its product physically interacts with Mre11. Deficiency in Nbs1 causes the clinical phenotype characterized by hypersensitivity to DNA damaging agents generating DSBs, through defective repair and checkpoint activation (Digweed et al., 1999; Matsuura et al., 2004; Tauchi et al., 2002; Varon et al., 1998).

Mre11 is an 80 kDa protein that harbors three constitutive phosphoesterase N-terminal motifs and one phosphoesterase motif similar to the SbcD subunit of the SbcCD nuclease (Fig. 2). It acts as an endonuclease that cleaves hairpin structures, as well as an exonuclease that degrades linear double-stranded (ds) DNA molecules (Biroccio et al., 2011; Sachs et al., 2011). The Mre11 phosphoesterase motifs are folded into a nuclease domain that exhibits 3′-5′ dsDNA dependent exonuclease activity and single-stranded (ss) and dsDNA dependent endonuclease activity on a variety of DNA substrates (Paull & Gellert, 1998; Trujillo et al., 1998). Curiously, the nuclease activities of Mre11 are not appropriate for the end-resection step required during HRR and recent observations suggest that the exonuclease activity of Mre11 is not involved in extensive DSB end-processing (Llorente & Symington, 2004). Krogh

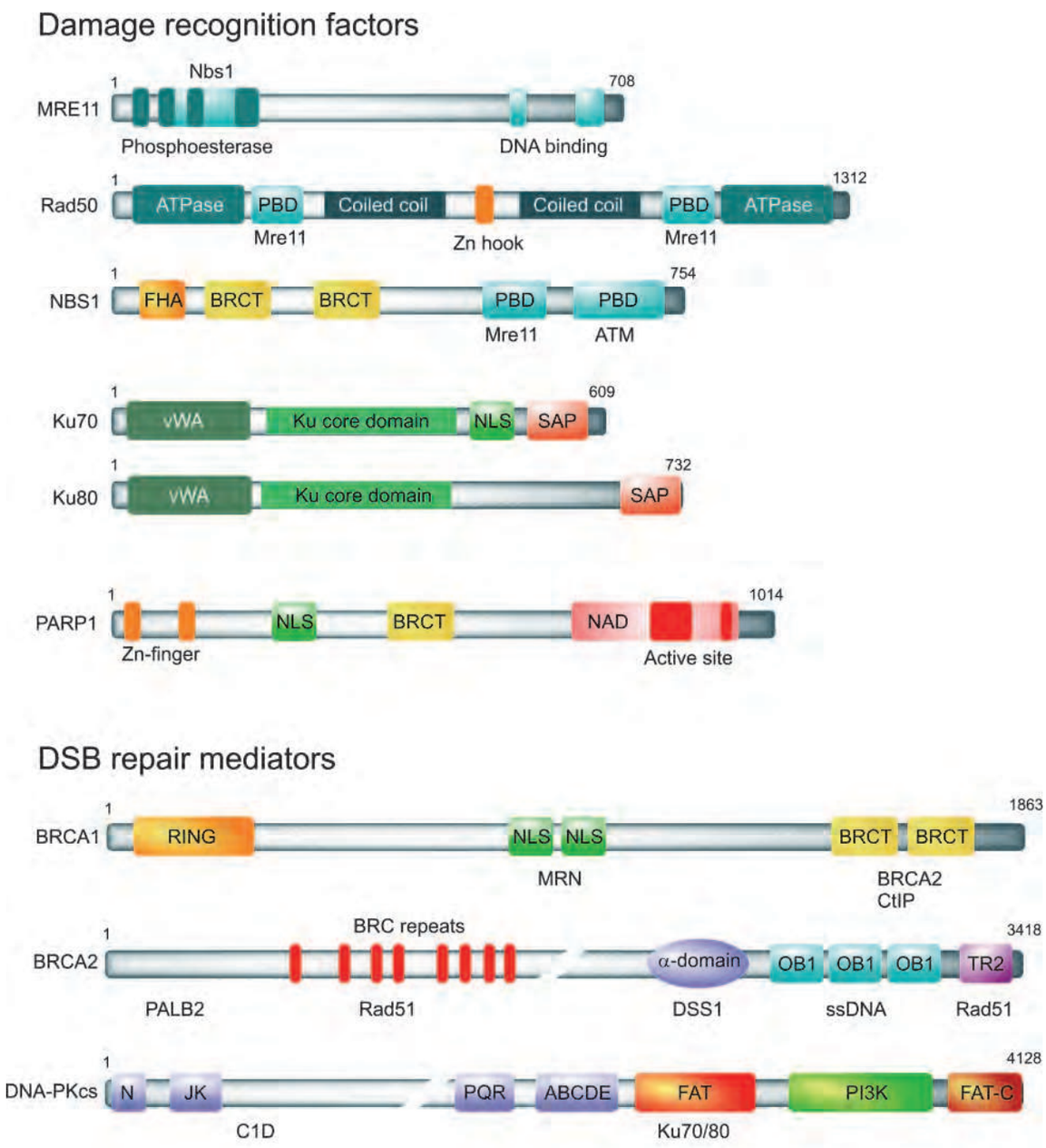


Fig. 2. Schematic representations of identified consensus domains in DSB repair proteins. Proteins participating in the initial steps of DSB repair and those considered to play a mediating role during signaling and repair are presented.

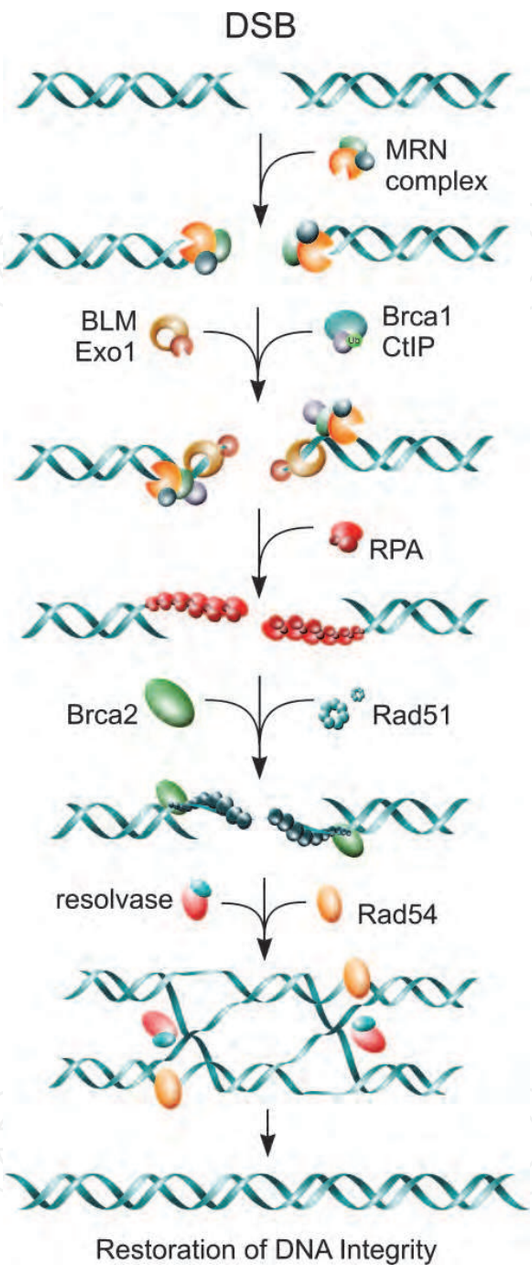


Fig. 3. Homology mediated repair of DSBs. The repair of DSBs by HRR is initiated by the resection of the DNA ends through the combined action of the MRN complex, the CtIP, ExoI and the BLM helicase, that catalyze the generation of 3' ssDNA regions and the formation of a Rad51 nucleoprotein filament - the structure involved in homology search. In subsequent steps and after localization of, and invasion into the homologous DNA region, repair synthesis is initiated and a HJ is generated from each DNA end, which in the end of the process is resolved by the resolvase complex.

and Symington have proposed a model, explaining the MRX (MRN) role in processing of DSB ends during meiosis or mitosis (Krogh & Symington, 2004). According to this model, Mre11 can execute its function through the cooperative action of an enzyme(s) with helicase and/or exonuclease activity. Through the action of such putative helicase the initial unwinding of DNA occurs, resulting in a formation of secondary DNA structures. In addition, Mre11 can process the 5' strand using its endonuclease activity by trimming the secondary DNA structures. Another enzyme with exonuclease activity might then catalyse the extensive resection of the 5′-end resulting in the generation of 3′-overhangs.

IR breaks the DNA molecule by damaging its sugar moiety, thus generating ends that are not amenable to ligation before processing. Mre11 may participate in such initial end processing but not in the final processing of the 5′ DNA strand. In agreement with this putative function, unmodified DSB ends generated by HO nuclease are substrates for nucleolytic enzymes even in the absence of active Mre11, suggesting that the nuclease function of MRN is only needed during the initial steps of the end-resection reaction. Studies in yeast have suggested that at least two nucleases (Exo1 and Dna2) in complex with a helicase (Sgs1) are involved in the end-resection step during HRR (Mimitou & Symington, 2009; Mimitou & Symington, 2008), but the functions of their mammalian homologs are incompletely characterized. However, it has been reported that the human homologue of the yeast resection factor Exo1, is important for the recruitment of RPA and Rad51 proteins through the generation of ssDNA regions. The potential role of Exo1 in HRR was also shown in experiments with Exo1 depleted cells, which develop hypersensitivity to ionizing radiation and show increased chromosomal instability (Bolderson et al., 2010). Moreover, the localization of Exo1 to DSBs depends on CtIP and MRN and its exonuclease activity is controlled by CtIP, supporting the idea that MRN is much more involved in the mediation of end-resection rather than in the direct digestion of 5′-DNA strand of the DSB (Eid et al., 2010).

After processing of the DNA ends, the generated single-stranded 3′-overhangs are covered by the RPA heterotrimer, the major mammalian ssDNA binding protein. During HRR, one of the functions of this protein is to protect ssDNA and to prevent the formation of secondary DNA structures (Fig. 3) (Fanning et al., 2006). However, RPA also mediates the recruitment of the ATR/ATRIP complex to the single stranded regions and initiates in this way the DDR signaling cascades, which among others inhibit cell cycle progression through activation of the corresponding checkpoints (Cimprich & Cortez, 2008; Zegerman & Diffley, 2009). Indeed, there is evidence that RPA functions as a checkpoint activator (Stephan et al., 2009), as well as a regulator of the repair process, possibly through shifts in its function by DNA damage-mediated post-translational modifications (Anantha et al., 2007; Vassin et al., 2009). RPA also facilitates indirectly Rad51 filament formation by mediating DNA-Rad52 or DNA-BRCA2 interactions (see below) (Mortensen et al., 2009; Thorslund & West, 2007). Genetic and biochemical data support the notion that HRR is driven by the proteins of *RAD52* epistasis group of genes, including Rad52, Rad54 and Rad51 with its paralogs (XRCC2, XRCC3, Rad51B, Rad51C and Rad51D) (Fig. 3) (Krogh & Symington, 2004; West, 2003). Along with its ability to promote the synapsis between the homologous DNA sequences, Rad51 arises as a central recombination protein facilitating in general the formation of hybrid DNA duplexes (Heyer et al., 2010). Rad51 interacts with RPA-coated single stranded 3′-overhangs to form a right-handed nucleoprotein filament. The nucleoprotein filament represents the active state of Rad51 recombinase and plays a pivotal role in the homology search reaction (Raderschall et al., 1999; West, 2003). The importance of

the *RAD51* gene in HRR was first shown in yeasts, where Rad51 deficiency is tolerated but Rad51 null cells exhibit an increased sensitivity to IR and to a variety of DNA damaging agents producing DSBs. These mutants also show defects in mitotic and meiotic recombination (Ofir et al., 2011; Shinohara et al., 1992).

The human *RAD51* gene was identified in 1993 by Morita et al., which have described a gene encoding a product sharing significant homology with bacterial RecA and ScRad51 recombinase (Morita et al., 1993). Despite extensive sequence similarity between human and yeast Rad51, the vertebrate Rad51 recombinase fails to complement the HR defects of yeast Rad51 mutants, suggesting evolutionary divergent properties for the two proteins (Shinohara et al., 1993). In contrast to lower eukaryotes, Rad51 is essential in vertebrates and *RAD51-/-* knockout mice die early during embryogenesis (Tsuzuki et al., 1996).

Rad51 exhibits ssDNA and dsDNA-stimulated ATPase activity, which drives the nucleation and extension of the Rad51 nucleoprotein filament. There is clear evidence that only Rad51-ssDNA nucleoprotein filament is able to catalyze DNA joint formation, supporting the assessment that Rad51 is recruited to ssDNA generated by nucleolytic processing of DNA termini (Ristic et al., 2005). Formation of Rad51 nucleoprotein filament also depends on a large number of factors controlling the effectiveness of HRR. One of the most important players mediating nucleation of Rad51 over DNA is Rad52 and BRCA2. While the Rad52 function is essential for yeast viability after IR (West, 2003), in mammalian cells BRCA2 substitutes Rad52 activity and plays more important role in the regulation of HRR than Rad52 (Davies et al., 2001; Thorslund & West, 2007; West, 2003). Nevertheless, both proteins are involved in the delivery of Rad51 monomers to the ssDNA overhangs in combination with the elimination of a negative effect of RPA on Rad51 filament formation (Thorslund & West, 2007). Notably, a BRCA2 homolog has not been identified in yeast, suggesting evolutionarily distinct requirements for HRR in yeast and in higher eukaryotes. The structural studies of BRCA2 and its orthologous proteins revealed a protein domain allowing DNA binding (Marmorstein et al., 2001; Zhou et al., 2009) and degenerative conservative motifs called the BRC repeats, physically interacting with Rad51 (Fig. 2) (Carreira et al., 2009; Carreira & Kowalczykowski, 2009; Davies et al., 2001). The structurally undisclosed TR2 motif in the extreme C-terminus of BRCA2 was found to play an important role in the regulation of Rad51 nucleoprotein filament formation and dissociation, and the binding of Rad51 to this motif is controlled by its phosphorylation at S3291 in a cell cycle dependent manner (Fig. 2) (Esashi et al., 2005; Esashi et al., 2007; Thorslund & West, 2007).

The formation of a Rad51 nucleoprotein filament marks the initiation of a pre-synaptic step of HRR, while strand invasion and the search for homology characterize the synaptic reaction (Fig. 3). After alignment of the invading DNA strand with the homologous DNA duplex, the chromatin remodeling functions of Rad54 and its homolog Rad54B operate to facilitate DNA synthesis and branch migration resulting in formation of double Holliday junctions when both processed 3'-overhangs invade the undamaged DNA molecule (Fig. 3) (Mazin et al., 2010). During the DNA repair synthesis step, sequence information is copied from the undamaged DNA molecule to the damaged one assisting thus its restoration. At the final stages of HRR the HJs are resolved by protein complexes identified as resolvases (Figure 3) (Liu et al., 2007; Mazina & Mazin, 2008; Symington & Holloman, 2008; West, 2009). While the resolution of the HJs by resolvases can lead to either gene conversion or crossing over, there is evidence that during repair of DSBs by HRR in higher eukaryotes gene conversion dominates.

3. When effectiveness is chosen over accuracy: DNA-PKcs dependent non-homologous end joining (D-NHEJ)

Perhaps surprisingly the above described high fidelity pathway of DSB repair, HRR, is utilized preferentially by prokaryotes and lower eukaryotes. Higher eukaryotes appear to preferentially utilize end joining to remove DSBs from their genome despite its error-prone nature. However, the reason for this preference remain hypothetical. Moreover, it is notable that vertebrates have extended their arsenal of end joining activities with a unique protein, the catalytic subunit of DNA-dependent protein kinase (DNA-PKcs) (Fig. 2), which is likely to play a role in this shift from HRR to NHEJ (Chen et al., 2011; Shibata et al., 2011). For this reason and in order to discriminate this pathway of NHEJ from other pathways of NHEJ that have recently surfaced (see below), we will refer to it in the remainder of this chapter as D-NHEJ. Other designations that can be found in the literature include "classical" or "canonical" NHEJ.

In principle, rejoining of DNA ends by NHEJ can be accomplished by standard ligation reactions, when ligatable DNA ends are present (Fig. 4). As pointed out above, simple end joining is not possible for IR induced DSBs, which therefore required end processing before ligation. In general, DSB repair by NHEJ is associated with limited or extensive additions or deletions of nucleotides at the generated junction, which alters the original DNA sequence at the damaged site (Marshall, 2011; van Gent & van der Burg, 2007). As a result, NHEJ is an error-prone repair pathway, which may be considered disadvantageous for higher eukaryotes, frequently opt for this repair mechanism. It is frequently reasoned that this risk may be mitigated by the excess of non-coding DNA in these organisms, which allows flexibility in terms of nucleotide substitutions, deletions or additions.

However, since DSBs are also generated randomly throughout the genome, they will also be induced in coding regions where changes in the nucleotide sequence are bound to have serious consequences.

Notably, there are also instances where the error prone nature of NHEJ is exploited to generate a specific biological result that requires sequence modification. Thus, addition or deletion of nucleotides during NHEJ associated with V(D)J recombination, increases the diversity of the antibodies generated (Lieber et al., 2006).

The importance of D-NHEJ factors in higher eukaryotes is indicated by diseases resulting from mutations in *Artemis*, *LIGIV* and *Cernunnos/XLF* genes. Thus, hypomorphic mutations in the *LIGIV* gene lead to severe immunodeficiency, radiosensitivity and developmental delay and account for the development of the LigIV syndrome (Chistiakov et al., 2009; Girard et al., 2004). Mutations in *Artemis* are associated with progressive radiosensitive severe combined immunodeficiency (RS-SCID) and patients with dysfunctional *Artemis* are characterized by increased radiosensitivity and impaired V(D)J recombination. DNA-PKcs deficient patients develop a classical SCID syndrome and show slight differences in their symptoms from *RAG* or *Artemis* deficient individuals (Hendrickson et al., 1991; Schuler & Bosma, 1989; van der Burg et al., 2009). The fact that most mutations in D-NHEJ genes are hypomorphic suggests that complete deletion of their activities is not compatible with human survival.

At the biochemical level, it is well documented that one of the most abundant cellular proteins, Ku, initiates NHEJ by binding to the ends generated at the DSBs (Lieber, 2010) (Fig. 4). Ku consists of two subunits, Ku70 and Ku86 (Ku80), which form a toroidal shaped

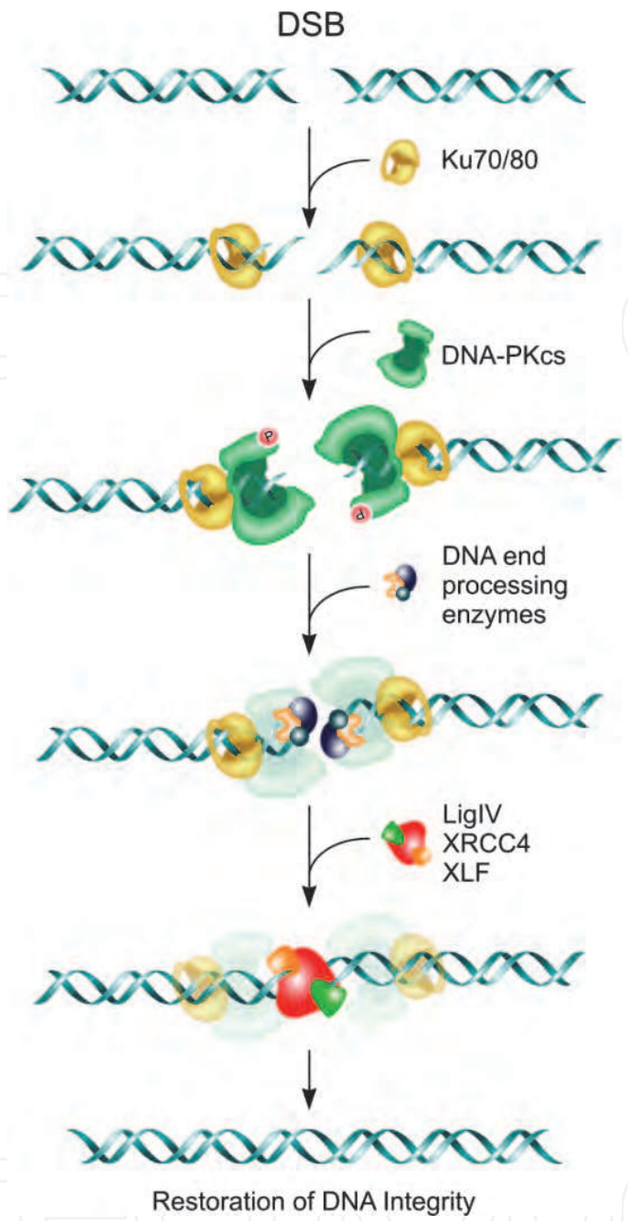


Fig. 4. Repair of DSBs by DNA-PKcs-dependent non homologous end joining. Major enzymatic activities involved in the repair of DSBs by the simple joining of the free DNA ends are depicted.

structure binding dsDNA with a variety of configurations at the ends. Once bound to DNA ends, Ku heterodimer changes its conformation and slides inward the DNA, thus attracting the catalytic subunit of DNA-PKcs to form an active DNA-PK holoenzyme (Meek, 2009; Meek et al., 2004). The activity of DNA-PKcs increases at least 10 fold upon interaction with the Ku-DNA complex (Lees-Miller & Meek, 2003). Therefore, D-NHEJ is greatly compromised in the absence of DNA-PKcs and, interestingly, under such conditions HRR is enhanced (Delacote et al., 2002; Shrivastav et al., 2009). However, more recent work points to inhibition of HRR in cells with altered or inhibited DNA-PKcs (Neal et al., 2011).

With its molecular weight of about 470 kDa, DNA-PKcs is by far the largest enzyme found to operate in D-NHEJ (Hill & Lee, 2010; Kirwan et al., 2011; Weterings & Chen, 2007). The enormous size of DNA-PKcs accommodates many important domains that may be involved in the regulation of its enzymatic activity and the interaction with other proteins (Fig. 2). DNA-PKcs is a serine/threonine kinase with specificity for S/TQ sites (Marshall, 2011) that regulates its activity through autophosphorylation. It targets, RPA2, WRN, Cernunnos/XLF, LigIV, and XRCC4 (Chen et al., 2000; Cruet-Hennequart et al., 2008; Otsuki et al., 2007; Soubeyrand et al., 2006; Yu et al., 2008). In addition to its catalytic function at the DSB ends, DNA-PKcs may also tether the broken DNA ends to facilitate rejoining (Meek et al., 2004). Although the DNA-PKcs kinase activity catalyzes the phosphorylation of many NHEJ related substrates, the phosphorylation of the DNA-PKcs itself is the only physiologically relevant event identified so far (Chen et al., 2000; Cruet-Hennequart et al., 2008; Otsuki et al., 2007; Soubeyrand et al., 2006; Yu et al., 2008). DNA-PKcs autophosphorylation appears to be important for DSB repair as DNA-PKcs mutated at key phosphorylation sites (T2609 and S2056 at ABCDE and PQR clusters respectively) is impaired in its function in D-NHEJ (Cui et al., 2005; Meek et al., 2007).

Elegant experiments demonstrate that DNA-PKcs autophosphorylation facilitates structural shifts, which allow other D-NHEJ end processing or ligation factors (polynucleotide kinase phosphatase, PNKP, terminal deoxynucleotidyl transferase, TDT, DNA polymerases λ and μ, LigIV/XRCC4/XLF complex) to be recruited to DNA ends (Kirwan et al., 2011). After end processing, two locally available DNA ends are joined through the coordinated action of the LigIV/XRCC4/XLF and the DNA-PK complexes and if the two sealed DNA ends originate from one DSB the integrity of the DNA molecule is restored (Ahnesorg et al., 2006; Wu et al., 2007; Yano et al., 2009) (Fig. 4). At present, it is not known whether as of yet uncharacterized functions incorporated into the NHEJ machinery have means of ensuring rejoining of the original ends. Available evidence is compatible with efficiently D-NHEJ joining any DNA ends, irrespectively of whether they belong to the same or to different DSBs. Such DNA end-promiscuity is considered the main cause of chromosomal translocations in repair proficient cells and may also contribute to the formation of chromosome aberrations in irradiated repair proficient cells (Iliakis et al., 2007).

4. An alternative pathway of non-homologous end joining with putative backup function (B-NHEJ)

Until relatively recently, D-NHEJ and HRR were considered as the only available pathways for removing DSBs from the genome. This raised the question of their coordination and labor separation under circumstances where both were active, as well as the function of each of them when the other was chemically or genetically compromised. The rationale was that when components of the one pathway were compromised residual DSB repair activity could be attributed to the function of the remaining active pathway. However, experiments testing this hypothesis failed to yield the expected results. Thus, although cells with mutations in genes encoding proteins involved in D-NHEJ exhibit a severe DSB repair defect, substantial residual rejoining is still detectable. Intriguingly, this rejoining activity does not rely on HRR, since cells with defects in this repair pathway show normal DSB repair as assayed by pulsed-field gel electrophoresis (PFGE) and HRR defects in D-NHEJ mutants fail to exacerbate their DSB repair phenotype. We speculated, therefore, the function of an additional DSB repair pathway based on end joining and functioning as backup (Fig. 5)

(DiBiase et al., 2000; Wang et al., 2003; Wang et al., 2001). This pathway is considered distinct and normally suppressed by D-NHEJ (Perrault et al., 2004), only coming to the fore whenever D-NHEJ is inactivated. We have proposed to term this form of end joining backup-NHEJ (B-NHEJ) in order to differentiate it from D-NHEJ and to indicate its putative backup function (Fig. 5) (Iliakis et al., 2004).

Extensive biochemical studies have provided evidence for the operation of B-NHEJ activities in *in vitro* end joining reactions. Thus, extracts of cells lacking DNA-PKcs showed normal end joining activity. However, the possible function of B-NHEJ to the repair of IR-induced DSBs received only limited attention until the demonstration that such pathways robustly substitute for D-NHEJ in class switch recombination in *LIG4* deficient mice (Soulas-Sprauel et al., 2007; Yan et al., 2007). Alternative pathways were also found to operate in V(D)J recombination in D-NHEJ deficient cells when mutations in *RAG1* and *RAG2* generate proteins forming DSBs without holding the DNA ends, which could then be processed by alternative repair pathways (Corneo et al., 2007; Jones & Simkus, 2009; Lee et al., 2004). Other reports subsequently showed near wild type CSR activity in *XRCC4* and *LIG4*-deficient mice associated with chromosome abnormalities at the *IgH* locus that hinted to the error prone nature of B-NHEJ (Soulas-Sprauel et al., 2007; Yan et al., 2007) (see below).

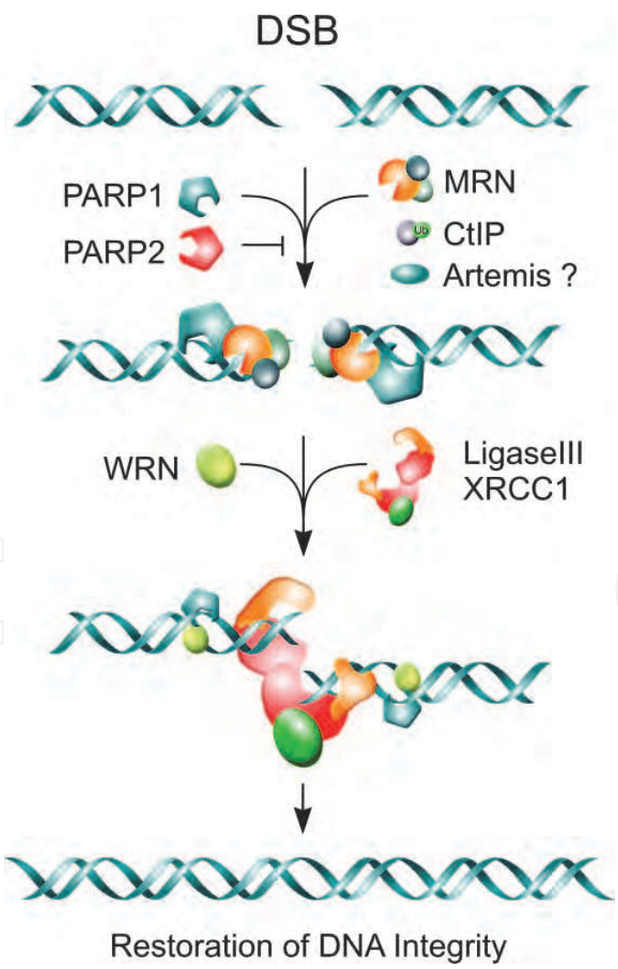


Fig. 5. Backup pathway of non homologous end joining.

These observations placed B-NHEJ not only at the forefront of DSB repair research but also at the center of carcinogenesis and led to an avalanche of studies describing its various characteristics. Various names were also proposed by different investigators including alternative NHEJ (A-NHEJ, or alt-NHEJ), microhomology-mediated end-joining (MMEJ), KU-independent end-joining, or LigIV-independent NHEJ (Corneo et al., 2007; Haber, 2008; Iliakis, 2009; Liang et al., 2008; Ma et al., 2003). We prefer to use the term B-NHEJ to emphasize its putative backup function. We anticipate that as the characterization of B-NHEJ proceeds and mechanistic information becomes available, better terms will develop reflecting important mechanistic properties of this repair pathway rather than arbitrarily selected phenomenological manifestations of the same.

A breakthrough in the characterization of factors involved in B-NHEJ was the identification of LigIII/XRCC1 complex as a key component (Wang et al., 2001a; Wang et al., 2001b). It is interesting that LigIII is only presented in vertebrates, where it also functions in the mitochondria (Ellenberger & Tomkinson, 2008; Tomkinson et al., 2006). Recent reports demonstrate that the essential functions of LigIII derive exclusively from its role in this organelle (Gao et al., 2011; Simsek et al., 2011). However, it remains open what contribution LigI might have on B-NHEJ and what kind of hierarchy exists between LigI and LigIII regarding to their functionality. LigIII has a broad substrate specificity and could participate in B-NHEJ via enzymatic activities outlined in the recently proposed "jackknife model" (Ellenberger & Tomkinson, 2008). According to this model the Zn-finger domain and the DNA-binding domain of LigIII act in a cooperative way to facilitate the ligation of DNA substrates with discontinuities in the sugar-phosphate backbone of the DNA.

As primary function of LigIII is considered the involvement in the repair of single-strand DNA breaks and base damages, where it operates with other proteins partners, it is therefore possible that the same interacting partners contribute to B-NHEJ. Principal candidate for promoting LigIII action during B-NHEJ, together with XRCC1, is Poly (ADP-ribose) polymerase 1 (PARP1). Indeed, we and others demonstrated that PARP1 operates in B-NHEJ (Audebert & Calsou, 2008; Audebert et al., 2006; Wang et al., 2006). It has also been demonstrated that PARP1 binds to DNA ends in direct competition with Ku heterodimer and may serve as a loading platform and coordinator of a subsequent steps of B-NHEJ (Wang et al., 2006). It is interesting in this regard that PARP1 and PARP2 are utilized in an AID-dependent manner during CSR in D-NHEJ deficient cells, suggesting that these proteins play a role in the processing of switch regions. However, it is not clear whether this function occurs as part of B-NHEJ (Robert et al., 2009). It is also notable that only PARP1 facilitates alternative end-joining mechanisms, while PARP2 actually suppresses translocations between *IgH* and *c-Myc* loci in D-NHEJ deficient B-lymphocytes (Robert et al., 2009).

Recently, histone H1 surfaced as an interesting factor involved in B-NHEJ (Rosidi et al., 2008). Although, histone H1 enhances the DNA end joining activities of both LigIV and LigIII, the enhancement of LigIII activity is significantly stronger. Further putative factors of B-NHEJ include the BCR/ABL protein. This protein is mutated in chronic myeloid leukaemia (CML), which results in stimulation of cellular proliferation, inhibition of apoptosis and altered cell adhesion. BCR/ABL may down-regulate D-NHEJ allowing thus the function of B-NHEJ. The latter would explain the genomic instability of leukemic cells (Poplawski & Blasiak, 2009). Other studies report a decrease in the level of key D-NHEJ proteins, Artemis and DNA LigIV and up-regulation of LigIII and Werner's syndrome protein (WRN) in CML cells (Sallmyr et al., 2008).

The frequent generation of non-ligatable DNA ends after IR suggests that resection might be involved in B-NHEJ. This function may be provided by end-processing factors like Mre11 and CtIP. Indeed, silencing of MRE11 in human fibroblasts decreases the frequency of global end-joining (Rass et al., 2009). Also, inhibition of MRE11 by mirin in XRCC4 and KU-deficient cells compromises B-NHEJ (Rass et al., 2009). Furthermore, mice lacking the entire MRN complex in their B cells are compromised in CSR mediated by both D-NHEJ and B-NHEJ (Dinkelmann et al., 2009). Recent reports also show that depletion of CtIP decreases the frequency of chromosomal translocations (Zhang & Jasin, 2011). Despite the above insights, the molecular mechanisms underpinning B-NHEJ are not fully understood and are at present under intensive investigation. Models have been proposed invoking microhomology (McVey & Lee, 2008). However, it is likely that the presence of microhomology at DNA ends is not a prerequisite for B-NHEJ; rather microhomology use may be a random event, determined by the nucleotide distribution along the dissected ends of the DSB (Simsek & Jasin, 2010). The level of dissection achieved is also likely to play a decisive role and the mechanisms regulating this dissection step deserve intensive investigation.

The accumulated data in the field allow the conclusion that deficiencies in the error-prone D-NHEJ pathway are associated with an increase in chromosomal translocations. Thus, B-NHEJ surfaces as a major determinant of chromosomal translocation formation in mammalian cells with potential contributions to carcinogenesis (Iliakis et al., 2007). Thus, B-cells deficient in D-NHEJ show frequent translocations between *IgH* and *c-Myc* loci (Boboila et al., 2010; Yan et al., 2007; Wang et al., 2009).

Notably, B-NHEJ appears to also be involved in telomere maintenance. Thus, depletion of TRF2, a known component of the shelterin complex, results in end-to-end chromosome fusions mediated by D-NHEJ, whereas depletion of TPP1–POT1a/b, another member of the shelterin complex, initiates robust chromosome fusions that are mediated by B-NHEJ (Rai et al., 2010).

In summary, B-NHEJ surfaces as an important pathway for the maintenance of the genome in higher eukaryotes. However, it exercises this function at the expense of fidelity. If modification of the sequence in the vicinity of the DSB is a weakness of D-NHEJ, hyper-recombination might be added as weakness of B-NHEJ.

5. Sharing the responsibility: coordination of DNA DSBs repair pathways and their cell cycle control and growth state dependencies

The fundamental differences between HRR and NHEJ and the error prone nature of the latter raise questions regarding their relative utilization and the principles applied to select one of them to repair a given DSB - beyond the obvious cell cycle specificity. This is because although HRR deficiency is not associated with a detectable defect in DSB repair as measured by PFGE, it is associated with increased radiosensitivity to killing, in many cases at magnitude similar to that observed with D-NHEJ mutants. This implies that HRR is a significant contributor to DSB repair. The following questions arise from the synthesis of these observations:

1. Why do cells opt for D-NHEJ for removing DSBs from their genome and how do they cope with induced changes in DNA sequence?
2. If HRR is involved in DSB repair, why is PFGE unable to detect a defect? Is it because it only processes a very small fraction (less than 10%) of the induced DSBs? Or is it

because unknown factors limit its contribution to low doses? Indeed, HRR mutants show a small defect in DSB repair when analyzed by scoring γ-H2AX foci (Rothkamm et al., 2003).

3. A frequently formulated hypothesis in the field is that D-NHEJ and HRR compete for DSBs and that pathway choice reflects the outcome of this competition. In line with this postulate, inactivation of NHEJ through mutations in the participating factors enhances some of the functions of HRR (Shrivastav et al., 2009). However competition between two so different repair mechanisms is difficult to rationalize. Are we missing something here? Notably, a situation reflecting competition between HRR and NHEJ is not detectable when the repair of IR induced DSBs is followed in different mutants (DiBiase et al., 2000; Wang et al., 2001)
4. The situation is now more complicated with the identification of B-NHEJ. How is B-NHEJ fitting in this overall picture and what does it really backs-up. Aspects of regulation of pathway selection and coordination are essential for our understanding of DSB repair and further investigations are warranted.

6. Conclusions

The importance of processing of DSBs generated in a programmed or accidental manner has been clearly demonstrated. Recent evidence emphasizes the role of a less known repair pathway, mechanistically and genetically distinct from the dominant DSB repair pathways, HRR and NHEJ. This pathway is capable of substituting almost entirely for D-NHEJ, but exhibits an increased propensity in rejoining wrong ends and in causing thus chromosome translocations. The characterization of factors involved in B-NHEJ and its integration to other pathways of DSB repair, as well as with DNA damage signaling and checkpoint activation, is expected to be vigorously pursued in the coming years. The fact that the function of B-NHEJ is associated with increased genomic instability leading to carcinogenesis is certain to provoke further investigations on the mechanisms of cancer development.

7. Acknowledgement

Work supported by grants from the European Space Agency (ESA) (AO-08-IBER), and the Bundesministerium für Bildung und Forschung (BMBF), Kompetenzverbund Strahlenforschung (KVSF) (02NUK005C, 02NUK001B).

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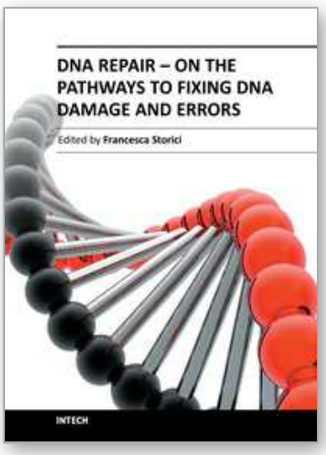
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DNA Repair - On the Pathways to Fixing DNA Damage and Errors
Edited by Dr. Francesca Storici

ISBN 978-953-307-649-2
Hard cover, 380 pages
Publisher InTech
Published online 09, September, 2011
Published in print edition September, 2011

DNA repair is fundamental to all cell types to maintain genomic stability. A collection of cutting-edge reviews, DNA Repair - On the pathways to fixing DNA damage and errors covers major aspects of the DNA repair processes in a large variety of organisms, emphasizing foremost developments, questions to be solved and new directions in this rapidly evolving area of modern biology. Written by researchers at the vanguard of the DNA repair field, the chapters highlight the importance of the DNA repair mechanisms and their linkage to DNA replication, cell-cycle progression and DNA recombination. Major topics include: base excision repair, nucleotide excision repair, mismatch repair, double-strand break repair, with focus on specific inhibitors and key players of DNA repair such as nucleases, ubiquitin-proteasome enzymes, poly ADP-ribose polymerase and factors relevant for DNA repair in mitochondria and embryonic stem cells. This book is a journey into the cosmos of DNA repair and its frontiers.

How to reference
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Emil Mladenov and George Iliakis (2011). The Pathways of Double-Strand Break Repair, DNA Repair - On the Pathways to Fixing DNA Damage and Errors, Dr. Francesca Storici (Ed.), ISBN: 978-953-307-649-2, InTech, Available from: http://www.intechopen.com/books/dna-repair-on-the-pathways-to-fixing-dna-damage-and-errors/the-pathways-of-double-strand-break-repair

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