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DNA Repair in Embryonic Stem Cells

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1. Introduction

DNA is the largest and most important molecule of a cell. Due to its chemical nature, DNA is particularly prone to numerous lesions. These lesions comprise different sugar and base modifications, deletion of bases as well as single (SSBs) and double DNA strand breaks (DSBs). All alterations in the DNA that a cell experiences sum up to more than 10.000 lesions per day (Lindahl, 1993). DNA damage can be brought about by several endogenous and exogenous factors including reactive oxygen species (ROS), ultraviolet light (UV), ionizing radiation (IR) or by DNA damaging chemicals. The different lesions are removed by several repair mechanisms that help the cell to preserve structure and sequence of the DNA. These repair pathways include mismatch repair (MMR), base excision repair (BER), nucleotide excision repair (NER), non-homologous end joining (NHEJ), microhomology-mediated end joining (MMEJ) and homologous recombination (HR). If DNA damage is too severe, cells can also initiate a cell death program that removes cells with damaged DNA from the population (reviewed in: Roos & Kaina, 2006).

Stem cells comprise a group of self-renewing cells including embryonic and adult stem cells. Embryonic stem cells (ESCs) have the ability of indefinite self-renewal and rapid proliferation. They are pluripotent and can differentiate into cells of all three germ layers (ectoderm, mesoderm and endoderm) as well as of the germ cell lineage. Adult or tissue stem cells, in contrast, are multipotent and differentiate into only one or several specific cell lines (reviewed in: Barilleaux et al, 2006; Thomson & Marshall, 1998; Weissman et al, 2001). By proliferation and differentiation, adult stem cells replenish tissue cells that are lost during normal wear and tear or after injury and thus are key for tissue and organ regeneration as well as for the preservation of homeostasis in a living organism (Reya et al, 2001). ESCs can be isolated from different species, but the most investigated ones are human (hESCs) and murine (mESCs) ESCs. Both, hESCs and mESCs are derived from the inner cell mass of a blastocyst, an early stage of embryonic development (Martin, 1981; Thomson et al, 1998). Human ESCs are of particular interest because of their high potential for medical applications like tissue and organ regeneration (reviewed in: Donovan & Gearhart, 2001; Thomson & Odorico, 2000; Wobus, 2001). However, since hESCs are derived from human embryos, they also raise ethical, social and juristic problems (McLaren, 2000). A potential alternative to the use of hESCs is the employment of induced pluripotent stem (iPS) cells. By transfection of a combination of stem cell markers, iPS cells can be made from basically every differentiated cell (Kim et al, 2009; Okita et al, 2007; Takahashi et al, 2007; Takahashi & Yamanaka, 2006; Wernig et al, 2007; Yu et al, 2007). Thus, differentiated cells can be taken from a patient, modified and induced for pluripotency *in vitro,* and transplanted back into

the same patient. Therefore, iPS cells are not only a great tool for research, they also allow an individualized therapy. Moreover, since donor and acceptor of the cells are the same individual, eventual problems with intolerance or rejection of the cells are prevented. Because of the low rate of reprogramming efficiency and the fact that several of the reprogramming factors are oncogenes, which bears the risk of a cancerous behavior of re-implanted iPS cells, this approach is, though, not as yet used extensively in therapy (Okita et al, 2007; Takahashi et al, 2007; Takahashi & Yamanaka, 2006).

The multitude of lesions that arise per cell and day illustrates that maintaining genomic integrity is an important issue for a cell. This applies even more for stem cells, which comprise the basal set of proliferating cells in an organism. Stem cells thus should have an even higher interest in preserving their genomic integrity than somatic cells. In line with this notion, stem cells have been reported to have to a higher rate of DNA damage-induced apoptosis and a lower frequency of mitotic recombination and mutations (Cervantes et al, 2002; de Waard et al, 2008; Momcilovic et al, 2010; Roos et al, 2007; Saretzki et al, 2004). These differences in the DNA damage response are due to variations in several parameters between stem cells and differentiated cells. One of the most intriguing dissimilarity between ESCs and differentiated cells is the short G1-phase and the absence of a G1 checkpoint in ESCs (Aladjem et al, 1998; Fluckiger et al, 2006; Hong & Stambrook, 2004). In addition, ESCs and differentiated cells vary in the expression of several repair genes (Maynard et al, 2008; Momcilovic et al, 2010; Tichy et al, 2011).

In this chapter we will review the current knowledge about DNA repair of ESCs, highlight differences to DNA repair of differentiated cells and discuss differentiation as an option of ESCs to respond to DNA lesions. Where necessary, we will discriminate between human and murine ESCs.

2. DNA damage recognition

Before damaged DNA can be repaired, the lesion must be detected. Therefore, specific "sensor" proteins are present in a cell, which scan across the DNA. When these sensor proteins find sugar or base modifications, SSBs or DSBs, they become trapped at the lesion and activated. These events mobilize further repair factors and initiate a signaling cascade that transduces the information about the lesion across the cell body. Well known "sensors" of lesions in the DNA are kinases of the PI3K-related kinase (PIKK) family including ataxia-telangiectasia mutated (ATM), ATM- and Rad3-related (ATR) and DNA-dependent protein kinase (DNA-PK; reviewed in: Oberle & Blattner, 2010). ATM, ATR and DNA-PK are specifically activated in response to double strand breaks. Once activated, these kinases initiate DNA repair and checkpoint signaling (Boehme et al., 2008; Bozulic et al., 2008; Dobbs et al., 2010; Motoyama & Naka, 2004; Shiloh, 2003).

One of the first events of differentiated cells in response to a double strand break is autophosphorylation of ATM at serine 1981 and phosphorylation of the histone variant protein H2AX at serine 139, thus generating γ-H2AX (Rogakou et al, 1999). Phosphorylation of H2AX then allows the formation of sub-nuclear structures that can be distinguished as "foci" by immunofluorescence microscopy (Rogaku et al., 1999; Burma et al, 2001; Ward & Chen, 2001). All three PIKKs, ATM, ATR and DNA-PK, phosphorylate H2AX when they are activated (Hammond et al, 2003; Stiff et al, 2004).

ESCs undergo similar events in response to DSBs as differentiated cells. In ESCs, ATM also becomes phosphorylated at serine 1981, relocates to DSBs and phosphorylates the histone

variant protein H2AX within a few minutes post irradiation (Momcilovic et al, 2009). Notably, mESCs display an elevated basal level of γ-H2AX, even in the absence of DSBs (Banath et al, 2009; Chuykin et al, 2008). Nevertheless, when H2AX phosphorylation is followed over time, mESCs and differentiated cells show a similar behavior with respect to foci formation and dissolution (Adams et al, 2010a; Chuykin et al, 2008). The reason for the high basal level of phosphorylated H2AX in mESCs is as yet unclear. A possible explanation is an eventually higher number of double strand breaks in mESCs, even in the absence of exogenous insults, which could result from global chromatin decondensation. Since most ESCs are in S-phase and replicating their DNA, the chromatin is usually kept in a more open structure and may therefore be more accessible for DSBs. Alternatively, the higher number of DSBs could result from an increased number of collapsed replication forks. It is known for several years that DSBs can derive from incomplete disaggregation of replication forks (Strumberg et al, 2000). Since one of the hallmarks of ESCs is their rapid proliferation, ESCs are almost constantly replicating their DNA, which enhances the probability of acquiring DSBs from collapsed replication forks during a given time. Another possibility for the high basal level of γ-H2AX foci is the elevated expression of ATM and ATR in ESCs, which could result in a higher phosphorylation activity even under normal growth conditions (Momcilovic et al, 2010). Besides H2AX, ATM phosphorylates CHK-2 at threonine 68, NBS-1 at serine 343, and TP53 at serine 15 in ESCs (Momcilovic et al, 2010).

In differentiated cells, ATM is mostly involved in the recognition of double strand breaks in response to ionizing irradiation and during the immune response, while ATR becomes activated by double strand breaks that are generated during replication (reviewed in: Cimprich & Cortez, 2008). Despite having similar targets in ESCs and differentiated cells, the division of labor between ATM and ATR appears to be somewhat different in these cell types. While ATM is the first choice for phosphorylation of H2AX after ionizing irradiation in differentiated cells and is absolutely required for the maintenance of genomic stability (Shiloh, 2003), the number of γ-H2AX foci after ionizing radiation was reduced to only thirty percent of wild type ESCs when ATR was genetically deleted albeit abundance of ATM was not altered under these conditions (Adams et al, 2010a). Similarly, inhibition of ATM by KU-55933 reduced NHEJ in hESCs by only twenty-five percent, whereas NHEJ rates were diminished under the same conditions by about fifty percent in neural precursors and by about seventy-five percent in astrocytes (Adams et al, 2010a). Genetic deletion of ATM or inhibition of the kinase yet impaired phosphorylation of ATM at serine 1981, of Tp53 at serine 15, of CHK-2 at threonine 68 and of NBS-1 at serine 343 as well as the implementation of a G2 arrest (Momcilovic et al, 2009).

Other "sensor" proteins recognize different kinds of DNA lesions. The XPA and XPC proteins, for example, recognize photoproducts and bulky adducts in the DNA that are generated upon exposure to UVB- and UVC-light or after exposure to certain chemicals. Glycosylases specifically recognize damaged bases, and heterodimers of MSH2/MSH6 and MSH2/MSH3 identify mismatches and short deletions in the DNA (Beard & Wilson, 2006; Iyer et al, 2006; Jiricny, 2006; Jones & Wood, 1993; Sugasawa et al, 2002). In accordance with the superior role of DNA repair in stem cells, the abundance of the mismatch sensors MLH2, MLH3 and MLH6 is significantly increased in ESCs. The increase in the amount of these repair proteins is at least partly due to enhanced transcription, although other mechanisms e.g. enhanced translation or protein stability may also contribute to the effect (Momcilovic et al, 2010; Osman et al, 2010; Roos et al, 2007; Tichy et al, 2011).

Another enzyme that acts as a DNA damage sensor and that functions in checkpoint signaling and in the preservation of genomic integrity is the poly(ADP-ribose) polymerase 1 (PARP-1), a protein that adds ADP-ribosyl moieties to substrate proteins including histone H1, DNA topoisomerase, DNA-PK and to PARP-1 itself (reviewed in: D'Amours et al, 1999; Shall & de Murcia, 2000). PARP-1 expression is also clearly elevated in mESCs (Tichy et al, 2010; V. Middel, unpublished data).

3. Base excision repair

Base excision repair (BER; Fig. 1) repairs modified bases, e.g. after oxidation or alkylation as well as abasic sites after spontaneous loss of bases (reviewed in: Fleck & Nielson, 2004; Zharkov, 2008). In principal, BER can be divided into two sub-mechanisms: short patch BER and long patch BER. Whereas short patch BER excises and replaces single nucleotides, long patch BER removes a stretch of several nucleotides (reviewed in: Robertson et al, 2009). Both sub-pathways start with the recognition of a damaged base by a DNA glycosylase and its excision, which leaves the DNA with an apurinic or apyrimidinic (AP) site. Proteins like apurinic/apyrimidinic endonuclease 1/redox effector factor 1 (APE-1/REF-1) then hydrolyze the 5'phosphodiesterbond in the sugar-phosphate backbone at the AP-site followed by insertion of a new base into the gap by DNA polymerase β and sealing of the break by DNA ligase III (reviewed in: Fleck & Nielson, 2004; Zharkov, 2008). Cells with lower APE-1/REF-1 activity are hypersensitive to several DNA damaging agents, including methylmethane sulfonate (MMS), hydrogen peroxide (H_2O_2), temozolomide (TMZ), ionizing radiation (IR) and cisplatin (Bapat et al, 2009; Fishel & Kelley, 2007; Ono et al, 1994). Since ESCs proliferate fast, they should produce a higher amount of ROS than differentiated cells, which should result in increased oxidation of bases and an increased amount of 8-oxoG, a damaged base that is normally removed from the DNA by the N-glycosylase/DNA lyase OGG1 (reviewed in: Boiteux & Radicella, 1999). In contrast to this expectation, very little 8-oxoG has been measured in undamaged hESCs (Maynard et al, 2008). The most simple explanation for this low amount of 8-oxoG would be a more effective removal of 8-oxoG in ESCs. However, neither elevated OGG1 protein levels nor enhanced enzyme activity have been observed in ESCs (Maynard et al, 2008). Another principle that could be used by hESCs to efficiently remove 8-oxoG would be recognition of 8-oxoG and initiation of its removal by other glycosylases. In consistency with this notion, other proteins of BER including Flap-endonuclease 1 (FEN-1), APE-1, X-ray repair complementing defective repair in chinese hamster cells 1 (XRCC-1), DNA ligase III, PARP-1 and Uracil-DNA-glycosylase 2 (UNG-2) are expressed in higher amounts in ESCs than in differentiated cells, while DNA-3-methyladenine glycosylase (MPG) is weaker expressed in hESCs than in differentiated cells (Fig.1; Table 1; Maynard et al, 2008; Momcilovic et al, 2010; Tichy et al, 2011, V. Middel, unpublished data). Surprisingly, despite the increase in several BER proteins and a strongly enhanced incision activity, overall BER activity is only moderately elevated in ESCs (Tichy et al, 2011).

4. Nucleotide excision repair

The nucleotide excision repair (NER) pathway preferentially removes bulky adducts and photoproducts from the DNA (Fig. 2). NER can be divided into three sub mechanisms which are transcription-coupled NER (TCR), global-genome NER (GGR) and transcription domain-associated NER (DAR) (reviewed in: Nouspikel, 2009). Defects in genes associated

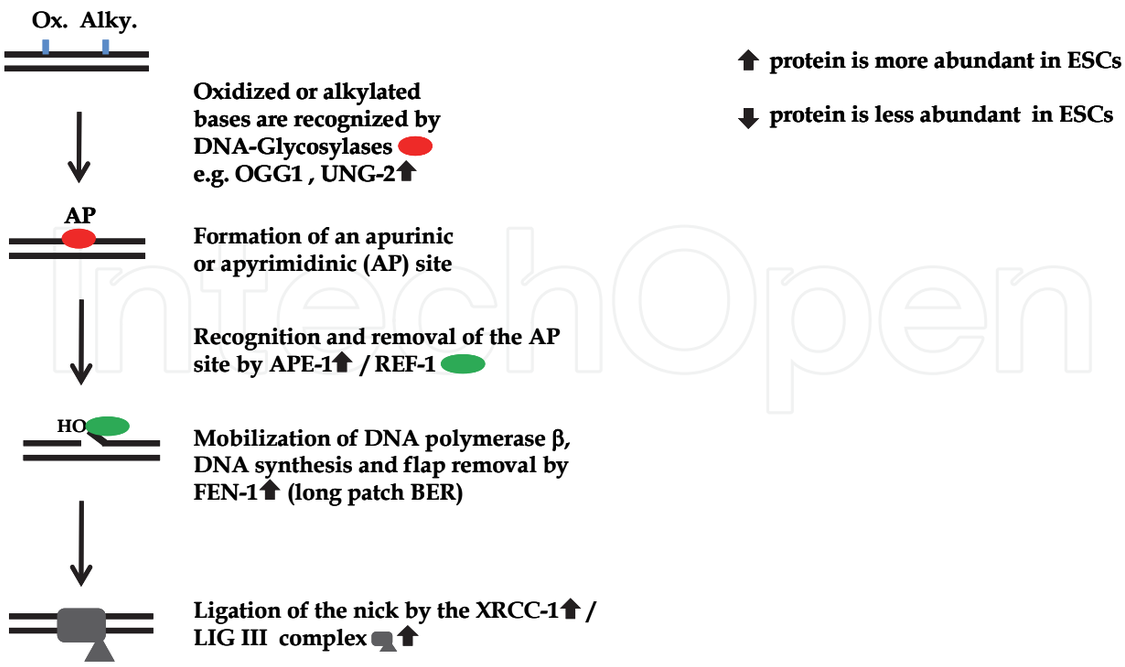

Fig. 1. Base excision repair (BER) in ESCs. Modified bases, e.g. after oxidation or alkylation are recognized by DNA glycosylases and excised, which leaves the DNA with an apurinic or apyrimidinic (AP) site. A complex of apurinic/apyrimidinic endonuclease 1/redox effector factor 1 (APE-1/REF-1) hydrolyses the 5'phosphodiesterbond in the sugar-phosphate backbone at the AP-site followed by insertion of one (short patch BER) or several (long patch BER) new bases into the gap by DNA polymerase β. Eventually occurring base overhangs are removed by flap-endonuclease 1 (FEN-1) prior to sealing of the break by the DNA ligase III (LIG III)/XRCC-1 complex. Arrows next to individual proteins indicate higher (⬆) or lower (⬇) abundance in ESCs.

with one of these pathways lead to several disorders including Xeroderma pigmentosum (XP), Trichothiodystrophy (TTD) and Cockayne syndrome (CS) (reviewed in: Nouspikel, 2009).
The first step in GGR is detection of the lesion by the XPC protein, usually due to an alteration in the helical structure of the DNA. This event mobilizes XPA and replication protein A (RPA) to the lesion, followed by recruitment of the ATPases/helicases XPB and XPD, which unwind the DNA double helix. The endonucleases XPG and XPF cut 3' and 5' of the lesion, leading to the release of a twenty-seven nucleotide (plus/minus two nucleotides) long stretch of DNA. Finally the gap is filled by DNA synthesis performed by DNA polymerase β and the nick is closed by DNA ligase I (Huang et al, 1992; O'Donovan et al, 1994; Riedl et al, 2003). TCR, in contrast, starts with recognition of the lesion by RNA polymerase II, which mobilizes CSA and CSB to the lesion. These proteins attract XPA and RPA, which initiate the same repair process as during GGR (reviewed in: Fousteri & Mullenders, 2008). DAR is a third sub-pathway of NER that has been particularly observed in terminally differentiated cells. In these cells, NER of non-transcribed regions is strongly compromised while transcribed regions are proficiently repaired. In contrast to TCR that only removes lesions in the transcribed strand, DAR also operates on the non-transcribed strand in transcriptionally active regions of the genome. Since DAR has been identified only recently, very little is known as yet about its mechanism (reviewed in: Nouspikel, 2009).

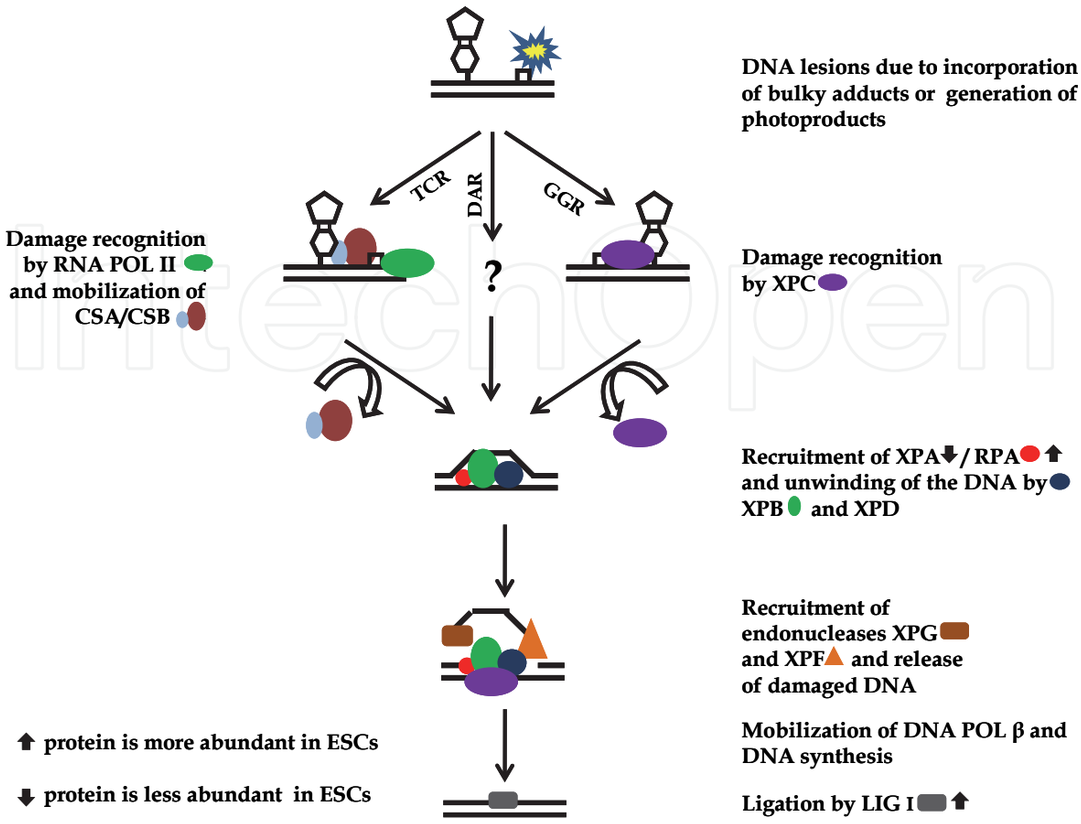

Fig. 2. Nucleotide excision repair (NER) in ESCs. The first step in global genome repair (GGR) is detection of the lesion by the XPC protein, usually due to an alteration in the helical structure of the DNA. This is in contrast to transcription-coupled repair (TCR), which starts with recognition of the lesion by RNA polymerase II (RNA POL II) and attraction of CSA and CSB to the lesion. These events mobilize XPA to the lesion, followed by recruitment of the helicases XPB and XPD which unwind the DNA double helix. The endonucleases XPG and XPF cut 3′ and 5′ of the lesion, leading to the release of a twenty-seven nucleotide (plus/minus two nucleotides) long stretch of DNA. Finally the gap is filled by DNA polymerase β (POL β) and the nick is closed by DNA ligase I (LIG I).The initial recognition step for DAR is as yet unknown. Arrows next to individual proteins indicate higher (⬆) or lower (⬇) abundance in ESCs.

Although most DNA repair pathways are more efficient in ESCs than in differentiated cells, for NER it appears to be the opposite (de Waard et al, 2008). While at low doses of UV-irradiation, MEFs and ESCs have comparable repair efficiencies, exposure to as little as 5 J/m² UVC leads to saturation of the repair capacity in ESCs (Van Sloun et al, 1999). Thus, although repletion is also an issue for differentiated cells, saturation levels are reached three times faster in ESCs than in MEFs (Van Sloun et al, 1999). At doses above 10 J/m² UVC-light, there is nearly no further repair of cyclobutane pyrimidine dimers (CPDs) and only about thirty percent of induced 6-4 photoproducts are repaired in ESCs within twenty-four hours. This is in strong contrast to MEFs or cardiomyocytes, which repair up to seventy percent of 6-4 photoproducts within twelve and more than fifty percent of CPDs in the transcribed region within twenty-four hours after irradiation (Cheo et al, 1997; van der Wees et al, 2003; Van Sloun et al, 1999; reviewed in: van der Wees et al, 2007). Eventually, the

decreased expression of XPA in hESCs contributes to the reduced repair activity, although this has not been seen in all cases (Maynard et al, 2008; Momcilovic et al, 2010). In contrast to XPA, the expression of RPA and DNA ligase I is enhanced in hESCs (Momcilovic et al, 2010), yet this might be due to the involvement of these repair proteins in other repair pathways.

It is known for several years that ESCs are less potent in NER than differentiated cells, but until more recently, it was unclear whether this failure is caused by inefficient GGR, TCR or by disorganization of both. With the establishment of mESCs and MEFs that are deficient in TCR (*csB-/-*), GGR (*xpc-/-*) or in both NER pathways (TCR/GGR; *xpa-/-*), this question could be solved. Genetic deletion of the *xpc* gene (GGR) further enhanced the number of apoptotic mESCs over the already high number of apoptotic ESCs after UV-irradiation, whereas genetic deletion of the *csB* gene (TCR) did not affect the rate of cell death of mESCs but significantly elevated their mutation rate after UV-exposure (de Waard et al, 2008). This is in contrast to differentiated cells where UV sensitivity is rather linked to TCR (Conforti et al, 2000; de Waard et al, 2008; Ljungman & Zhang, 1996; Ljungman et al, 1999). The difference between ESCs and differentiated cells might be due to different responses of the transcriptional machinery to photoproducts in the DNA. While RNA synthesis is rapidly blocked in differentiated cells after exposure to UV light, gene transcription is continued for several hours in mESCs, even after irradiation with up to 10J/m^2 (de Waard et al, 2008).

5. Mismatch repair

The mismatch repair (MMR, Fig. 3) pathway is focused on the repair of mispaired nucleotides, arising after exposure to chemical agents like the methylating agent N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) or after errors during replication (reviewed in: Marra & Jiricny, 2005). Mismatches in the DNA are recognized and processed by a heterodimer of MSH2 and MSH3 or MSH6. The MSH2/MSH6 heterodimer supports repair of bases and mismatches with one or two unpaired nucleotides, while the MSH2/MSH3 heterodimer initiates repair of up to ten unpaired nucleotides and is rather inefficient in the identification of single nucleotide mismatches. Loss of function due to mutations in MMR genes leads frequently to hereditary nonpolyposis colorectal cancer (HNPCC), one of the most common cancers in the Western World (Fishel et al, 1993; Leach et al, 1993). MMR defective mice also showed spontaneous lymphomas upon exposure to DNA damaging agents as well as sterility and microsatellite instability (Friedberg & Meira, 2006).

After recognition of the DNA lesion by MSH2/MSH3 or MSH2/MSH6, a heterodimer of MLH1 and PMS1, MLH1 and PMS2 or of MLH1 and MLH3 is recruited to the damaged site. ATP-binding to MSH2/MSH3 or to MSH2/MSH6 verifies mismatch recognition, recruits MUTL to the lesion and initiates further repair activities. Other proteins that are required for MMR are proliferating cell nuclear antigen (PCNA), exonuclease 1 (EXO-1), RPA, replication factor C (RFC), high mobility group box 1 protein (HMGB-1) and DNA polymerase δ (POLδ). These proteins associate with MSH2, MSH3, MSH6 and/or MLH1 and are required for MMR initiation, excision of the mismatch and for DNA re-synthesis (reviewed in: Iyer et al, 2006; Jiricny, 2006; Li, 2008).

MMR is strongly enhanced in mESCs, which correlates with elevated expression of the MMR genes *msh-2*, *msh-3*, *msh-6*, *mlh-1*; *pms-2*, *mutyH* and *exo-1* (Fig. 3; Table 1), enhanced binding to damaged DNA and increased mismatch repair activity (Momcilovic et al, 2010; Osman et al, 2010; Roos et al, 2007; Tichy et al, 2011). DNA repair, however, seems to be not

the only function of MMR proteins. Overexpression of MSH2 also strongly reduced survival of 3T3 cells in response to treatment with the alkylating agent MNNG, while genetic deletion of the gene increased resistance to cell killing by low level irradiation and alkylating or oxidizing drugs in ESCs (Abuin et al, 2000; DeWeese et al, 1998; Roos et al, 2007). Thus MSH2 and eventually other mismatch repair proteins may also be involved in the induction of apoptosis. The high abundance of some of these repair proteins in ESCs may therefore also contribute to the increased sensitivity of stem cells towards alkylating and oxidizing agents.

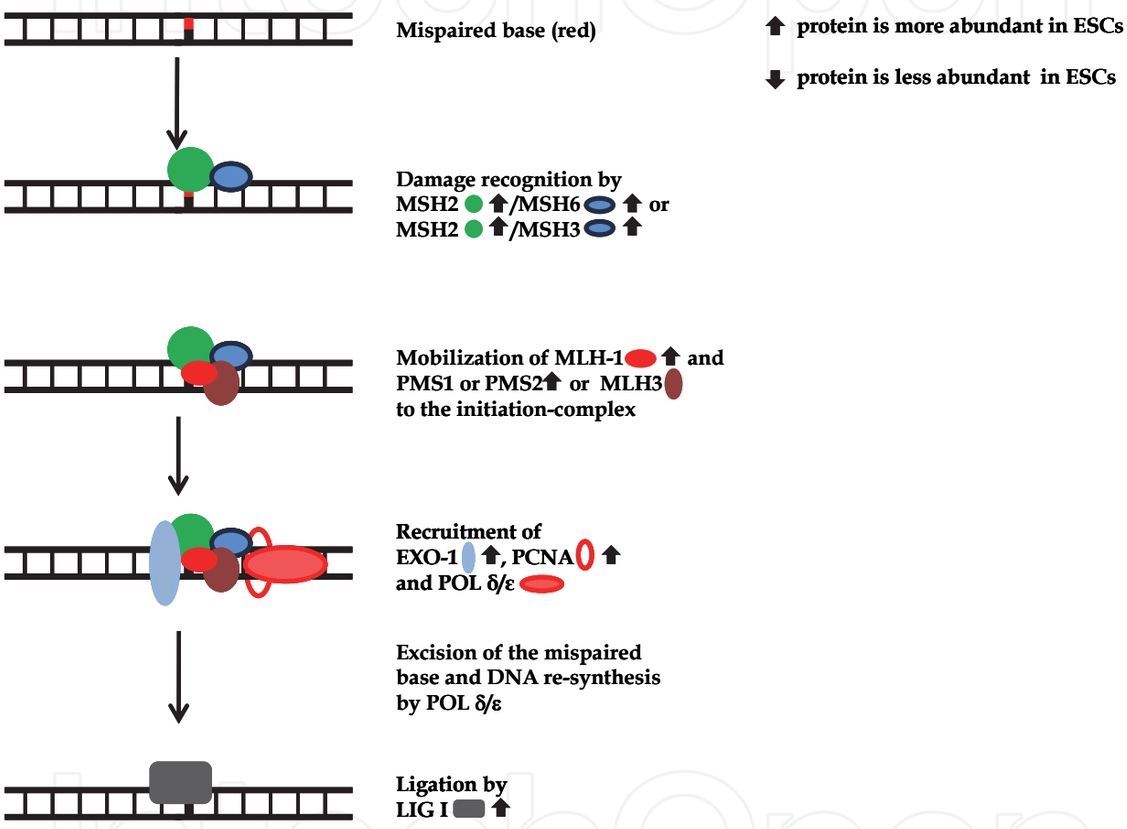

Fig. 3. Mismatch repair (MMR) in ESCs. After recognition of DNA lesions by MSH2/MSH3 or MSH2/MSH6, a heterodimer of MLH1 and PMS1, MLH1 and PMS2 or of MLH1 and MLH3 is recruited to the damaged site. Other proteins that are required for MMR are proliferating cell nuclear antigen (PCNA), exonuclease 1 (EXO-1), and DNA polymerase δ/ε (Pol δ/ε), which synthesizes the missing base(s). The final ligation step is performed by DNA ligase I (LIG I). Arrows next to individual proteins indicate higher (↑) or lower (↓) abundance in ESCs.

6. Repair of DNA double strand breaks by homologous recombination and non-homologous end joining

Double strand breaks (DSBs) can occur through normal cell metabolism, as intermediates of programmed genome rearrangements or after exposure to DNA damaging agents such as

ionizing radiation (IR). If not properly repaired, DSBs can result in chromosomal rearrangements and other severe genetic abnormalities as well as in senescence and apoptosis (reviewed in: Cahill et al, 2006). Because of the severe genomic aberrations that can arise, DSBs are considered as being the most harmful DNA lesion. Nonetheless, DSBs are also introduced into DNA on purpose, for example as part of the "mating-type-switch" in *Saccharomyces cerevisiae* or during V(D)J recombination in the course of the maturation of B- and T- cells in mammals (reviewed in: Paques & Haber, 1999; Soulas-Sprauel et al, 2007). DSBs are repaired by two major repair pathways: homologous recombination (HR; reviewed in: Johnson & Jasin, 2001) and non-homologous end joining (NHEJ; reviewed in: Lieber, 2008). HR is usually accurate, while NHEJ is frequently error-prone.

NHEJ starts with the recognition of the DSB by the Ku70/Ku80 heterodimer, a protein complex that binds specifically to broken DNA ends (Fig. 4). Once bound, Ku70/80 recruits the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) to form the DNA-PK holoenzyme. The DNA ends, which often posses damaged bases, are then processed by nucleases such as Artemis or the MRN (Mre11, Rad50, Nbs1) complex. Finally, a complex of XRCC-4 (X-ray repair complementing defective repair in chinese hamster cells 4), DNA Ligase IV and XLF (XRCC4-like factor) seals the break (Ahnesorg et al, 2006; Valerie & Povirk, 2003). HR starts with the recruitment of RAD51 to the DSB and resection of the broken DNA resulting in the generation of single stranded DNA (ssDNA; Fig. 5). RPA then binds to the exposed ssDNA to form a nucleoprotein filament and RAD51 mediates invasion of the nucleoprotein filament into the homologues duplex DNA and formation of a D-loop (Baumann et al, 1996; Sung et al, 2003). The 3'-end of the invading strand is extended by DNA polymerase during branch migration, the Holliday junctions are resolved and the emerging nicks are ligated by DNA ligase I (reviewed in: Heyer et al, 2010).

A major difference in the repair of DSBs between ESCs and differentiated cells lies in the use of the two main pathways for DSB repair, HR and NHEJ (Fig. 6). While somatic cells repair DSBs mostly through NHEJ and less frequently via HR, this is opposite in ESCs, which repair seventy-five to eighty percent of DSBs by HR and only fifteen to twenty percent by NHEJ (Francis & Richardson, 2007; Yang et al, 2004). One reason for the prevalent use of HR by ESCs is the short G1 phase of the cell cycle (Fig. 7). Hence, almost seventy percent of an ESC population is in S-phase (Fluckiger et al, 2006; Savatier et al, 2002). Therefore, a significantly greater number of ESC chromosomes have sister chromatids available that can be used for HR. However, it should be noted that ESCs use HR even in the G1-phase of the cell cycle to repair DSBs (Serrano et al, 2011).

According to the importance of HR in ESCs, the RAD51 protein is about 20 times more abundant in ESCs than in differentiated cells and ES cells exhibit a higher number of cells with Rad51 foci after irradiation (Sioftanos et al, 2010; Tichy et al, 2010; Tichy & Stambrook, 2008). In addition, hESCs express a larger isoform of RAD51 (Adams et al, 2010a). Within several minutes after irradiation, RAD51 foci are observed in hESCs, which reach a maximum at six hours after irradiation. This is different, e.g. to neuronal progenitor cells, which also form RAD51 foci within minutes after irradiation, but in neuronal progenitor cells, it takes about twelve hours for maximal foci formation (Adams et al, 2010a). However, since in MEFs RAD51 foci are already maximally formed at four hours after irradiation (Sioftanos et al, 2010) and thus much earlier than in mESCs, these differences in the kinetics might rather display species- and cell type-specific differences than differences between stem cells and differentiated cells. Beside RAD51, RAD52, EXO-1 and MRE11 are also more abundant in ESCs than in differentiated cells (Table 1; Momcilovic et al, 2010; Tichy et al, 2010).

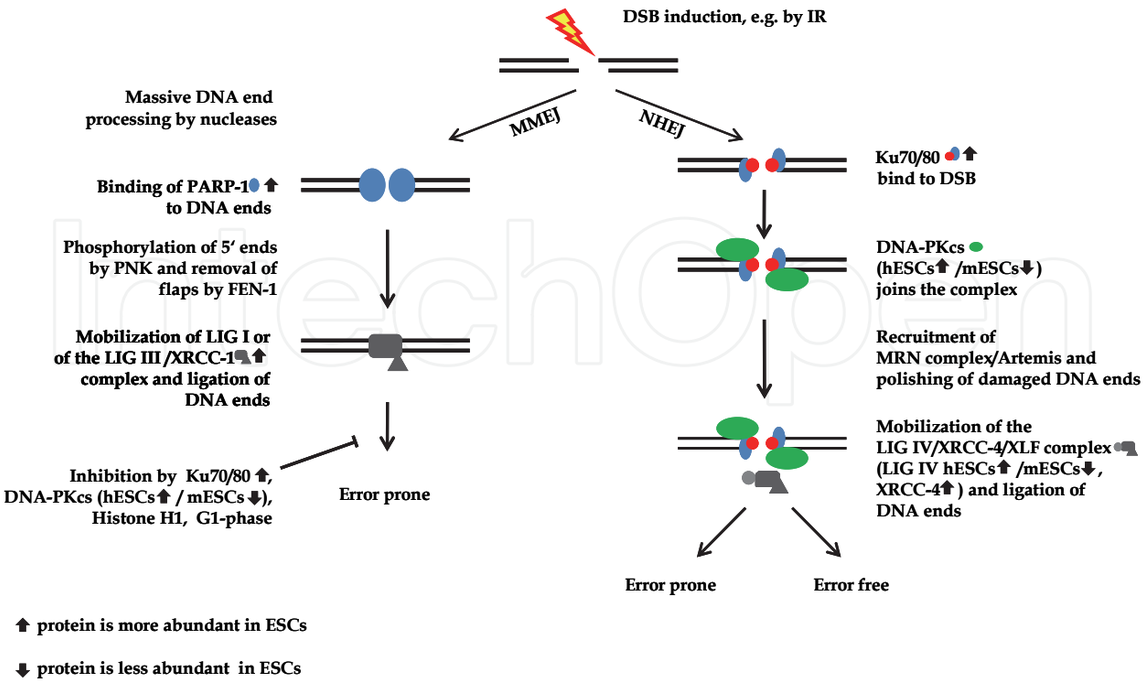

Fig. 4. DSB End joining pathways in ESCs. DSBs can be repaired by two end joining pathways. Microhomology-mediated end joining (MMEJ) starts with massive end processing by cellular nucleases and binding of poly(ADP-ribose) polymerase 1 (PARP-1) to the DNA ends. Binding of PARP-1 mobilizes further DNA end processing enzymes like polynucleotide kinase (PNK) and flap-endonuclease 1 (FEN-1). Finally, Ligase I (LIG I) or a heterodimer of Ligase III and XRCC-1 (LIG III/XRCC1) are attracted for the final ligation step. Proteins like Ku70/Ku80, DNA-PKcs and Histone H1 inhibit MMEJ. Non-homologous end joining (NHEJ) starts with binding of the Ku70/80 heterodimer to broken DNA ends. DNA-PK_{CS} translocates to the DSB and binds to the Ku complex. Afterwards, nucleases such as the MRN complex and Artemis arrive at the lesion and polish the DNA ends. Ligation of the DNA is performed by a complex of DNA ligase IV (LIG IV), XRCC-4 and XLF. Arrows next to individual proteins indicate higher (⬆) or lower (⬇) abundance in ESCs.

Despite the high rate of HR in ESCs for repair of DSBs they also use NHEJ, yet at a low rate. Lesions repaired by NHEJ can feature deletions or insertions of up to several thousand basepairs (Boubakour-Azzouz & Ricchetti, 2008). Genetic deletion of XRCC-4, downregulation of DNA-PK by siRNA or inhibition of DNA-PK activity by small molecules further reduced NHEJ frequency in hESCs, yet to a lesser extent than in differentiated cells (Adams et al, 2010a; Adams et al, 2010b), further supporting the notion that ESCs perform NHEJ, to some extent. In line with the infrequent use of NHEJ is the weak expression of the catalytic subunit of DNA-PK (*dna-pk*$_{CS}$) in mESCs, albeit the kinase is strongly expressed in hESCs (Banuelos et al, 2008; Momcilovic et al, 2010). In contrast to *DNA-PK*$_{CS}$, *ku70* and *ku80* are highly expressed in hESCs and mESCs (Maynard et al, 2008; Momcilovic et al, 2010; Tichy et al, 2010). A potential explanation for the different expression levels of *dna-pk*$_{CS}$ and *ku70* and *ku80* could be that Ku70 and Ku80 might have additional functions in ESCs. The Ku70/Ku80 heterodimer, for example, impedes unwanted recombination processes of

chromosomes and thus reduces mutation rates (Gullo et al, 2006). In addition, the Ku70/Ku80 heterodimer is involved in the regulation of cell growth and G1/S transition, where it keeps p21 levels under control, as well as in DNA replication, where it binds to origins of replication and associates with the replication machinery (Matheos et al, 2003; Matheos et al, 2002; Rampakakis et al, 2008). The repair factor XRCC-4 is expressed in similar amounts in mESCs and differentiated cells, while DNA ligase IV is less abundant in mESCs (Tichy et al, 2010). Only little is known about the principles that regulate the differential abundance of these proteins. However, as RNA levels of DNA ligase IV do not differ between mESCs and differentiated cells (Tichy et al, 2010), abundance of the proteins should be regulated posttranscriptionally.

In addition to cell type-specific differences in the expression of repair factors, there are also species-specific dissimilarities. XRCC-4, for example, is present in similar amounts in mESCs and MEFs, while in hESCs its expression is elevated compared to differentiated cells (Momcilovic et al, 2010; Tichy et al, 2010). Also DNA ligase IV is present in higher amounts in hESCs compared to differentiated human cells (Momcilovic et al, 2010), while its expression is lower in mESC compared to differentiated cells (Tichy et al, 2010). In contrast, DNA-PK_{CS} is present in lower amounts in mESCs compared to MEFs (Banuelos et al, 2008), but its expression is elevated in hESCs in comparison to differentiated human cells (Momcilovic et al, 2010). Also expression of breast cancer 1 (*BRCA-1*), a tumor suppressor protein which is involved in cell cycle regulation, transcription and DNA repair, is much lower in mESCs than in differentiated murine cells (Figure 8), while it is present in higher amounts in hESCs than in differentiated human cells (Table 1; Momcilovic et al, 2010).

7. Microhomology-mediated end joining (MMEJ): an alternative pathway to NHEJ and HR in ESCs

An alternative pathway related to NHEJ is microhomology-mediated end joining (MMEJ; Fig. 4). This repair pathway is, though, very error-prone due to massive DSB end processing and it leads frequently to deletions and occasionally to chromosomal aberrations like insertions, inversions or translocations (reviewed in: McVey & Lee, 2008). While for NHEJ one to five complementary bases are sufficient for the initiation of repair, MMEJ requires ten to twenty-five complementary bases (reviewed in: McVey & Lee, 2008). Preferred substrates for MMEJ are DSBs with blunt and non-cohesive ends, which are poor templates for NHEJ (Zhang & Paull, 2005). Proteins like PARP-1, XRCC-1, the bifunctional polynucleotide phosphatase/kinase (PNK), DNA ligase I and DNA ligase III are major players in this repair pathway (Zhang & Paull, 2005).

After introduction of a DSB, PARP-1 becomes active and is recruited to the DSB where it attracts PNK and the DNA ligase III/XRCC-1-complex. When these proteins are at the lesion, PNK phosphorylates the 5'-end of the DNA at the DSB. After that, the DNA ends are ligated by the DNA ligase III/XRCC-1-complex (Audebert et al, 2004; Audebert et al, 2006; Audebert et al, 2008). Apart from the "core" MMEJ-factors, Ku70, Ku80, Histone H1, CtIP (CtBP-interacting protein), CDK-2, and BRCA-1 are involved in MMEJ, albeit Ku70, Ku80 and Histone H1 are mostly active as regulators of this repair pathway (reviewed in: McVey & Lee, 2008). While Ku70 inhibited MMEJ in fission yeast (*Schizosaccharomyces pombe*), Ku80 promoted MMEJ in CHO (chinese hamster ovary) cells (Decottignies, 2007; Katsura et al, 2007). It remains to be determined whether these two proteins, that usually function as a heterodimer,

regulate MMEJ indeed differently or whether the opposing observations are due to species-specific variations. Also Histone H1 suppresses MMEJ, while CtIP, a component of the CtIP/BRCA-1/MRE-11 complex, supports DSB end resection, an essential process during MMEJ in somatic cells (Liang et al, 2005; Zhong et al, 2002).

There is very little known about the regulation of MMEJ in ESCs, yet, MMEJ is used in ESCs, albeit at a very low frequency (Tichy et al, 2010). Eventually, it only serves as a backup repair system in case of severe damage or when proteins of the classical NHEJ pathway are not available. A possible explanation for the minor contribution of MMEJ to DSB repair in ESCs might lie in the error-proneness of this repair pathway. Since ESCs are masters of preserving their genomic information, MMEJ might not be an appropriate pathway for DNA repair in general in this cell type.

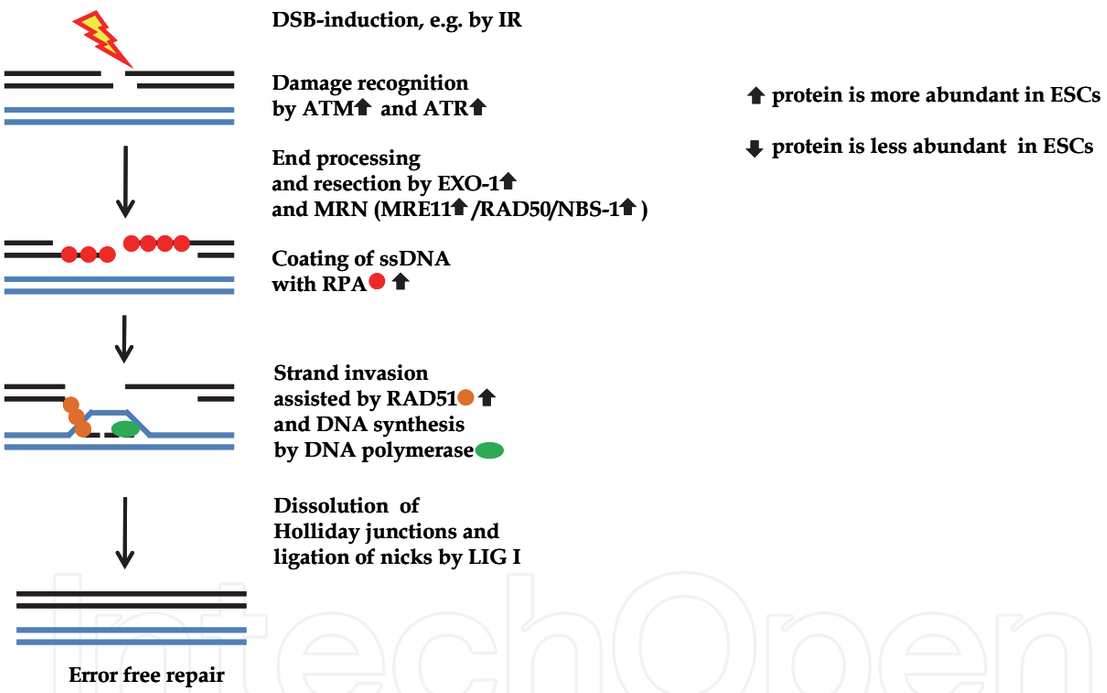

Fig. 5. Homologous recombination in ESCs. DSBs are recognized by ATM and ATR. DSB ends are resected by 5`-3` exonucleases like Exonuclease I (EXO-1) or the MRN complex, resulting in single stranded DNA ends (ssDNA). RPA binds to ssDNA and protects the DNA ends from degradation. Then, RAD51 is mobilized and binds to ssDNA followed by the formation of a presynaptic complex and displacement of RPA. Rad51 finally invades into the sister-chromatid and DNA polymerase synthesizes new DNA using the corresponding sister-chromatid as a template. At the end, Holliday Junctions are dissolved by resolvases and the nicks are ligated by DNA ligase I (LIG I). Arrows next to individual proteins indicate higher (⬆) or lower (⬇) abundance in ESCs.

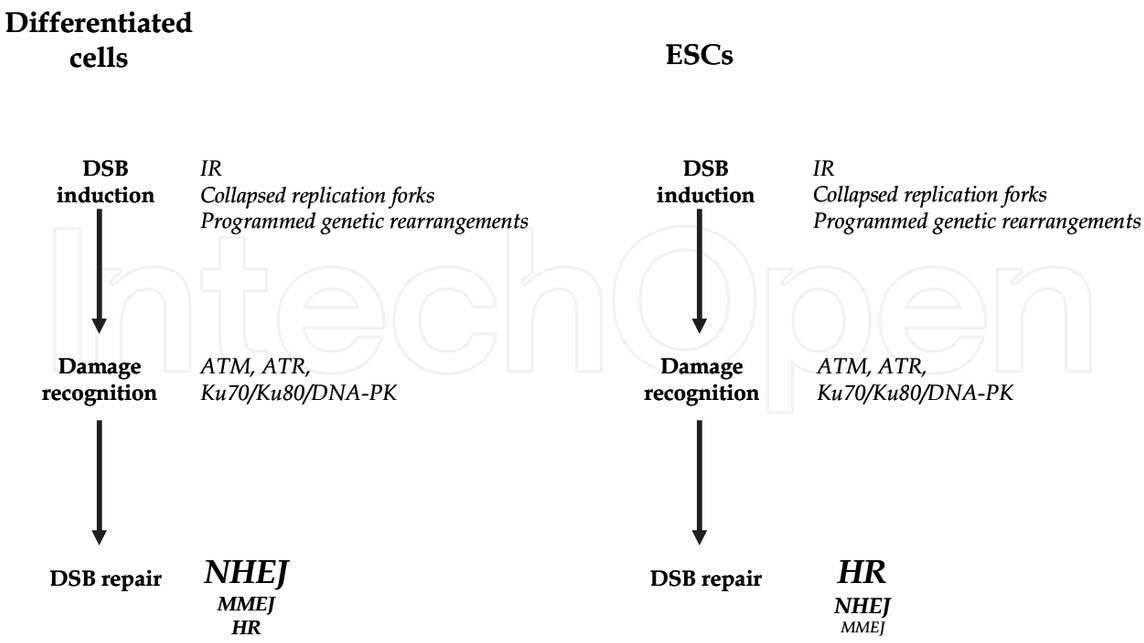

Fig. 6. Double strand break repair in somatic versus embryonic stem cells. After DSB induction, lesions are detected by ATM, ATR or the Ku70/Ku80/DNA-PK complex and repair pathways are switched on. While somatic cells predominantly repair DSBs by non-homologous end joining (NHEJ) and only secondary by microhomology-mediated end joining (MMEJ) and homologous recombination (HR), ESCs favour homologous recombination for DSB repair.

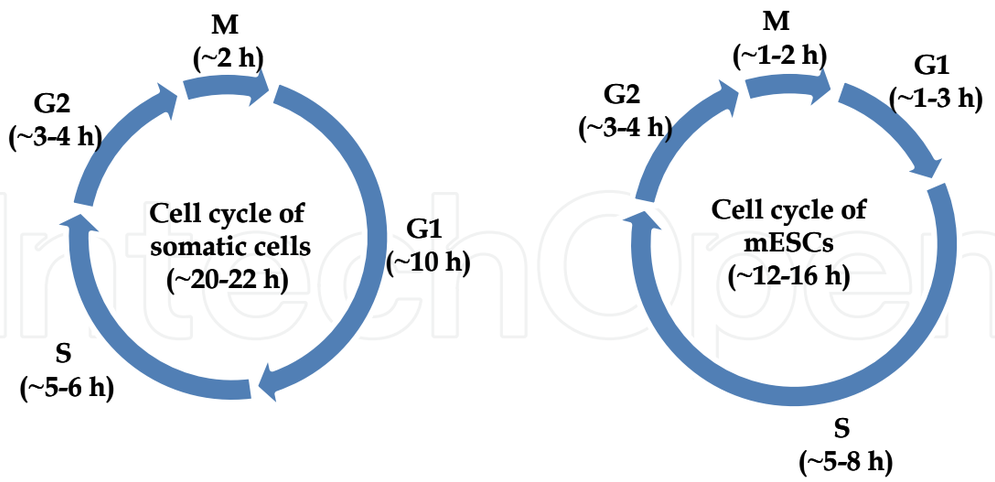

Fig. 7. Duration of the cell cycle of somatic cells and embryonic stem cells. In differentiated cells, progression through the cell cycle takes about twenty-four hours (h) whereas, due to a very short G1-phase it takes only about twelve hours in mESCs. Due to the short G1-phase, S-phase becomes automatically the longest phase of the cell cycle of ESCs resulting in about seventy percent of ESCs of a proliferating population in S-phase (Aladjem et al., 1998; Savatier et al., 2002; Hong and Stambrook, 2004; Fluckiger et al., 2006).

8. Induction of differentiation in response to DNA damage

Differentiation is a way for ESCs to respond to a negatively changing environment or growth condition. During differentiation, stem cells loose their potential to proliferate while they remain vital and functional as a differentiated cell. Differentiation is therefore an attractive option for stem cells to respond to DNA damage, when repair is not possible or has been unsuccessful. Since cell division is discontinued, DNA lesions and mutations cannot be propagated to daughter cells while the cell can still fulfill some functions. Nevertheless, under conditions of severe DNA damage, induction of cell death might certainly be the better choice to maintain a healthy population of ESCs.

There are several routes by which differentiation can be initiated after DNA damage. One option is via activation of the tumor suppressor protein Tp53. Upon DNA damage, the transcription factor Tp53 accumulates in the nucleus of stem cells (Lin et al, 2005; Solozobova et al, 2009). Among the promoters, to which Tp53 binds upon activation is the promoter of *nanog*, an important stem cell marker gene. Binding of Tp53 suppresses transcription of *nanog* and elimination of the Nanog protein from stem cells, leads to their differentiation (Lin et al, 2005). Activation of Tp53 can, however, also have the opposite effect as activated Tp53 also stimulates production of the Wnt ligands Wnt3, Wnt3a, Wnt8a, Wnt8b and Wnt9a (Lee et al, 2010). The Wnt ligands are secreted from cells with damaged DNA and engulfed by neighboring ESCs, where they inhibit differentiation (Lee et al, 2010). In consequence, these cells continue to proliferate, which may help to maintain a healthy pool of ESCs and to replace cells that are lost by apoptosis after genotoxic insults. Another route to differentiation in response to cellular stress is via activation of the c-Jun-N-terminal kinase (JNK). JNK is a negative regulator of the gp130-JAK-STAT3 signaling cascade in somatic cells (Lim & Cao, 1999), a pathway that also controls pluripotency in stem cells (Raz et al, 1999). Since JNK is activated in response to DNA damage (Adler et al, 1995; Nehme et al, 1999; Wilhelm et al, 1997), it is conceivable that this signaling pathway also supports differentiation of stem cells in the presence of DNA lesions. A further signaling cascade that is involved in regulating differentiation in hESCs is the NFκB pathway (Yang et al, 2010). Since DNA damage also activates NFκB (Basu et al, 1998), it may influence stem cell differentiation also via this route.

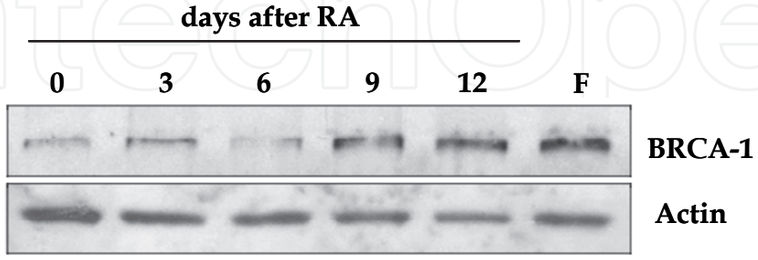

Fig. 8. Expression of BRCA-1 in mESC and during differentiation. D3 cells were treated with retinoic acid for the indicated time. Four hours prior to harvest, MG132 was added to the cultures. Cells were lysed and the amount of BRCA-1 was determined by Western Blotting. Hybridization with an antibody directed against actin served for loading control.

	Proteins			References
	abundance	mESCs	hESCs	
BER	⬆	APE-1, DNA ligase III, PARP-1, PCNA, UNG-2, XRCC-1	DNA ligase III, Endonuclease III-like protein 1 (gene: *NTHL1*), PCNA, UNG-2, FEN-1, XRCC-1	Maynard et al, 2008; Momcilovic et al, 2010; Tichy et al, 2010, 11
	⬇	-	DNA-3-methyladenine glycosylase (gene: *MPG*)	Maynard et al, 2008; Momcilovic et al, 2010
NER	⬆	-	DNA ligase I, RPA	Maynard et al, 2008; Momcilovic et al, 2010; Tichy et al, 2010
	⬇	-	XP-A	Maynard et al., 2008
MMR	⬆	MLH-1, MSH-2, MSH-6, PCNA PMS-2	EXO-1, MSH-2, MSH-3 MSH-6, A/G-specific adenine DNA glycosylase (gene: *MUTYH*), PCNA,	Momcilovic et al, 2010; Roos et al, 2007;
	⬇	-	Three prime repair exonuclease 1 (gene: *TREX1*)	Momcilovic et al, 2010
HRR	⬆	FEN-1, PCNA, γ-H2AX, RAD51, RAD52, RAD54	ATM, ATR, BRCA-1, FEN-1, DNA-ligase I, MRE11, NBS-1 (gene: *NBN*), PCNA, RAD51, RAD52, RPA, XRCC-2	Chuykin et al, 2008; Jirmanova et al, 2005; Maynard et al, 2008; Momcilovic et al, 2010; Tichy & Stambrook, 2008; Tichy et al, 2010
	⬇	BRCA-1	-	Fig. 8
NHEJ	⬆	γ-H2AX, Ku70, Ku80, PARP-1, PCNA, RAD54, XRCC-1	ATM, ATR, BRCA-1, DNA ligase IV, DNA-PK_{CS}, Ku70, Ku80, MRE11, PCNA, XRCC-4	Banuelos et al, 2008; Chuykin et al, 2008; Jirmanova et al, 2005; Maynard et al, 2008; Momcilovic et al, 2010; Tichy & Stambrook, 2008; Tichy et al, 2010
	⬇	BRCA-1, DNA-PK_{CS}, DNA ligase IV	-	Banuelos et al, 2008; Tichy et al., 2010; Fig. 8
MMEJ	⬆	DNA ligase III, PARP-1, PCNA, XRCC-1	DNA ligase III, PNK, PCNA, XRCC-1	Maynard et al, 2008; Momcilovic et al, 2010; Tichy et al, 2010

BER: Base excision repair, NER: Nucleotide excision repair, MMR: Mismatch repair, HR: Homologous recombination, NHEJ: Non-homologous end-joining, MMEJ: Microhomology-mediated end-joining.

Table 1. Comparison of the expression of genes involved in DNA repair between hESCs and their differentiated counterpart and mESCs and differentiated murine cells. Whether the abundance is increased in ESCs in relation to the differentiated counterpart (⬆) or decreased (⬇) is indicated with either black or blue arrows.

9. Conclusions

It is known for many years that ESCs acquire significantly less mutations and genetic rearrangements in response to DNA damage than differentiated cells. This observation raises the interesting possibility that, by understanding how DNA repair is controlled in stem cells, one could eventually make DNA repair in differentiated cells more efficient and less error-prone. This would eventually help to reduce the accumulation of DNA lesions in the cells and thus combat development of cancer and degenerative diseases and to reduce failures associated with aging. Comparison of the DNA damage responses of ESCs and differentiated cells has shown that ESCs are not only more sensitive to DNA damaging agents, they usually also use the available repair pathways more efficiently and they prioritize error-free repair pathways over error-prone ones. This different behavior is also reflected in differences in the expression of repair proteins. Currently it is unclear, which factors are responsible for the different expression pattern of repair proteins and how they are regulated in stem cells and differentiated cells. One possibility that has been discussed in the past is that, due to the short G1 phase of the cell cycle, a significantly higher number of stem cells are in S-phase compared to differentiated cells. Accordingly, stem cells have higher levels of the transcription factor E2F-1 (Roos at al, 2007). It has, however, only been shown for very few repair proteins, that their expression is indeed controlled by E2F-1. In addition, it needs to be resolved whether the differences in the expression of some repair pathways is indeed the reason for a more effective repair or whether this is only co-incidence. Here, more research is needed to identify the regulatory factors and their interplay.

Another important issue is the sporadically observed species-specific difference in the expression of repair factors. Are these differences indeed due to species-specific gene expression programs or do we eventually look at different types of cells? Although murine and human ESCs are both derived from the inner cell mass of a blastocyst, it is presently unclear how far they are really comparable. A close look at origin and culture conditions of the employed cells is certainly required to allow a direct comparison of the gene expression program and behavior of different stem cell lines.

A matter that we have not addressed in this review is DNA repair of iPS cells, since only a minor amount of data is currently available on DNA repair of these cells. However, since iPS cells are presently intensively investigated for future therapeutic applications, research into DNA repair capabilities of reprogrammed cells is of prime importance.

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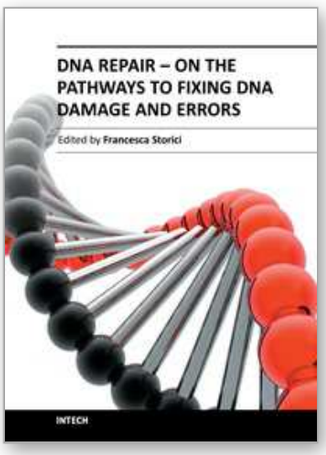

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