Review Article

Protein kinase CK2 in DNA damage and repair

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Abstract: Protein kinase CK2, formerly known as casein kinase 2, is a ubiquitously expressed serine/threonine kinase, which is absolutely required for cell viability of eukaryotic cells. The kinase occurs predominantly as a tetrameric holoenzyme composed of two regulatory α or α' subunits and two non-catalytic β subunits. It is highly expressed and highly active in many tumour cells. The proliferation promoting as well as the anti-apoptotic functions have made CK2 an interesting target for cancer therapy. It phosphorylates numerous substrates in eukaryotic cells thereby regulating a variety of different cellular processes or signalling pathways. Here, I describe the role of CK2 in DNA damage recognition followed by cell cycle regulation and DNA repair. It turns out that CK2 phosphorylates a number of different proteins thereby regulating their enzymatic activity or platform proteins which are required for recruiting proteins for DNA repair. In addition, the individual subunits bind to various proteins, which may help to target the kinase to places of DNA damage and repair. Recently developed pharmacological inhibitors of the kinase activity are potent regulators of the CK2 activity in DNA repair processes. Since DNA damaging agents are used in cancer therapy the knowledge of CK2 functions in DNA repair as well as the use of specific inhibitors of CK2 may improve cancer treatment in the future.

Keywords: Protein kinase; DNA repair; DNA damage; cell cycle; phosphorylation; protein-protein interactions

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Introduction

Human chromosomes are constantly under pressure from various DNA damaging agents, such as ultraviolet light (UV), reactive oxygen species, ionizing radiation and a lot of different chemicals in the environment (1). These various insults create DNA single or double strand breaks and various modifications of bases in the nucleotides. Furthermore, there are defects generated naturally by thermally induced alterations in purine- and pyrimidine bases as well as mutations induced by DNA replication (*Figure 1*). The cellular response to DNA damage includes three general steps i.e., (I) recognition of DNA damage; (II) intra-cellular signalling leading to cell cycle arrest; (III) DNA repair. DNA damage is recognized by various sensors, which then usually induce a variety of cellular signalling pathways including pathways that regulate cell cycle arrest giving the cell time to repair the damage. Depending on the DNA damage various repair mechanisms are known such as base excision repair, nucleotide excision repair, mismatch repair, homologous and non-homologous end joining, just to mention but a few (2,3) (*Figure 1*). Among the many proteins which are implicated in the recognition of DNA damage and the following cellular signalling are protein kinases such as the phosphatidylinositol-like kinases ATM, ATR and DNA-PK (1,3). These and many other kinases phosphorylate a variety of down-stream effectors many of which are recruited to the DNA damage, are somehow implicated in cell cycle arrest or are necessary for DNA repair. Mutations in the genes coding for these kinases result in embryonic lethality or strong cancer predisposition. Among the human kinome over the last 10 years protein kinase CK2 has attracted the attention of many scientist because this enzyme seems to be required for cell viability (4). The amount and the enzyme activity of CK2 are elevated in cancer cells (5). Furthermore, more and

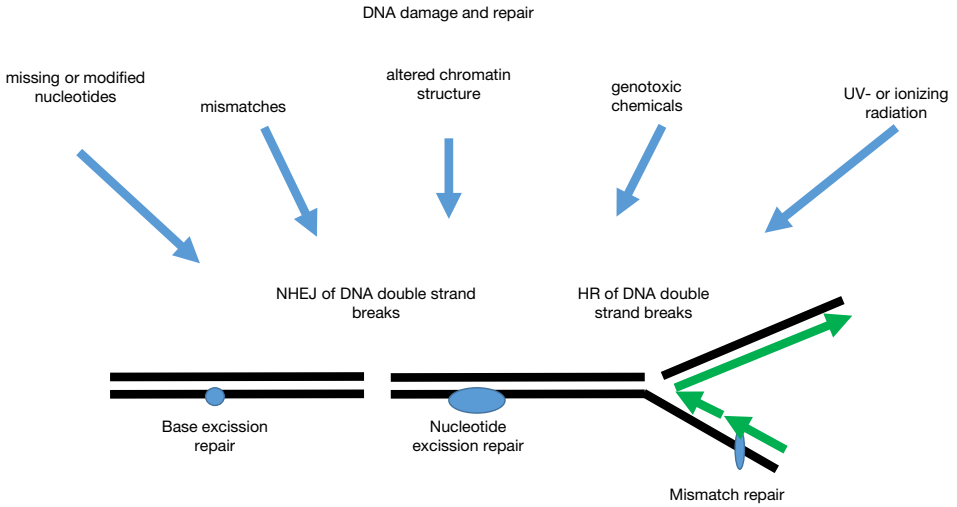

Figure 1 CK2 and mismatch repair. Mismatches are recognized by MsH1/MsH6 which are substrates of CK2. DNA damage and repair. Factors which induce DNA damage are listed. The scheme shows different DNA damages and the appropriate DNA repair mechanisms.

more inhibitors of the kinase activity were detected which are partially useful drugs for the treatment of cancer (6,7). In the present review I will focus on the role of protein kinase CK2 in DNA damage recognition, subsequent signalling and DNA repair.

More than 60 years after the first description of its enzymatic activity protein kinase CK2 is still an enigma. It is implicated in a variety of different cellular processes such as regulation of cell proliferation, apoptosis, signal transduction, development and differentiation, regulation of transcription, angiogenesis, carbohydrate metabolism and protein biosynthesis just to mention but a few (4,8-12). There is a steadily increasing number of different substrates in nearly every compartment of a eukaryotic cell (13,14). Thus, CK2 seems not to be implicated in the regulation of one particular single pathway but it seems to modulate many different pathways depending on the subcellular localisation, interacting proteins and the cell species (14,15). CK2 is composed of two catalytic α- or α'- subunits which are encoded by distinct genes on different chromosomes (16) and two non-catalytic β-subunits to form the CK2 holoenzyme. In addition, there is increasing evidence for functions of the individual CK2 subunits aside from the holoenzyme (17) (and literature therein) and moreover, there is also some evidence that the activity of CK2 is regulated by aggregation into higher molecular complexes. Although primarily classified as a serine/threonine kinase, CK2 also phosphorylates tyrosine residues (18-20).

Since CK2 is for a long time known to be implicated in so many cellular processes such as regulation of life and death of a cell, cell proliferation and cell cycle regulation it was not surprising that already 20 years ago the first reports appeared demonstrating also a role in genotoxic stress response.

CK2 influence on chromatin structure

Post-translational modifications including phosphorylation of histones are known to modify the histone-DNA interactions. CK2 phosphorylates histone H4 at serine 1 and it was further shown that this phosphorylation slightly affected the efficiency of DNA double-strand break repair by non-homologous end joining (21,22). On the other hand a histone H4 serine 1 mutant did not show any elevated sensitivity to DNA damage. Instead, it was shown that an elevated serine 1 phosphorylation by CK2 correlates with histone de-acetylation (22).

Shortly after DNA damage histone H2AX is phosphorylated and this phosphorylation is an early known marker of DNA damage. CK2 was found to co-localize with phospho H2AX (γH2AX) at sites of DNA strand breaks. Down-regulation of CK2α and CK2α' by small interfering RNAs (siRNAs) and treatment of the cells with a radiomimetic compound revealed a higher level of γH2AX which might indicate a higher level of DNA strand breaks (23). Proximity ligation assays (PLA assays) showed a co-localization of γH2AX

and CK2α' demonstrating one of the very rare functions of CK2α'. Phosphorylated γH2AX recruits other proteins to the site of DNA damage in order to activate DNA repair. Another protein which is recruited to sites of DNA damage is the heterochromatin protein HP1-β also named CBX1. This protein is bound to histone H3 which is methylated at lysine 9. CK2 phosphorylation seems to be implicated in HP1-β mobilization and γH2AX phosphorylation. Thus, these data point to a CK2 mediated signalling mechanism that initiates the DNA damage response by altering the chromatin structure (24,25).

Recently, it was shown that the number of DNA single strand breaks did not depend on pre-treatment of the cells with a CK2 kinase inhibitor, namely TBB (26). This might indicate that CK2 does not play a significant role for DNA damage induction. Instead it was found that the disappearance of foci was delayed after inhibition of the CK2 kinase activity as measured by γH2AX focus formation. The authors speculated that CK2 might regulate the γH2AX dephosphorylation by its ability to regulate the PP2A phosphatase (27). Alternatively, CK2 phosphorylation of HP1-β in response to DNA damage might play a role in the regulation of γH2AX phosphorylation (24).

CK2 and cellular signalling

The first indication for a role of CK2 in the cellular response to DNA damage stems from an experiment described in 1990 where a cDNA coding for CK2α complemented the UV-sensitivity of an immortalized Xeroderma pigmentosum cell line to an UV resistant level (28). Since transfection of CK2α into these cells resulted in an increase in CK2 protein kinase activity the authors speculated about the possibility of a cellular response to DNA damage by CK2 dependent protein phosphorylation. The first substrate which was identified as a CK2 substrate and CK2 binding partner implicated at least indirectly in DNA repair was the growth suppressor p53 (29-32). Interestingly, binding between CK2 and p53 was mediated by the β-subunit of CK2 which led to a down-regulation of the p53 transactivation function. On the other hand, binding of wild-type p53 to CK2 down-regulated the CK2 kinase activity whereas a transforming mutant of p53 enhanced CK2 kinase activity (31-34). p53 was found to promote the rapid annealing of complementary RNA and DNA strands, whereas pre- incubation of p53 with CK2 completely inhibited the p53 annealing activity (32). In other experiments it was shown that arsenite inhibited an UVB induced phosphorylation of human p53 at the CK2 phosphorylation site serine 392 (35). This inhibition corresponded to a suppression of the p53 DNA binding activity and transactivation function. The authors speculated that arsenite may act as a co-carcinogen by targeting p53 thus, inhibiting DNA repair. Other DNA damage inducing factors such as psoralen and UVA also modify human p53 at amino acid 392 (36-39). Mutation of serine 389, which is the corresponding CK2 phosphorylation site in mouse p53, led to enhanced UV-induced skin cancer which indicates a tumour-suppressing role of p53 in UV-induced DNA damage (40). Keller *et al.* identified an UV-activated protein complex which contained CK2 and the chromatin elongation factor FACT (facilitates chromatin transcription). FACT is a heterodimer containing hSpt16/cdc68 and SSRP1 (structure-specific recognition protein 1) (41). This UV-activated protein complex specifically phosphorylated serine 392 of human p53 and thereby enhanced the sequence- specific DNA binding of p53 at least *in vitro* (42,43). The enhanced DNA binding activity correlated with an elevated transcriptional activity of p53 in response to UV. Later on maize SSRP1 was identified as a substrate for CK2 (44). This phosphorylation induced the recognition of UV-damaged DNA.

Recognition of the DNA damage induces a signalling cascade which is started by the PI3-kinase-like kinases ATM, ATR and DNA-PK followed by the down-stream checkpoint effector kinases Chk1, Chk2 and Chk3 (MK2). One of the cell cycle regulating kinases and down-stream targets of Chk1 and Chk2 is cdk1 which is phosphorylated by CK2 at amino acid serine 39 (45). Furthermore, phosphorylation of other substrates by these PI3-kinase-like kinases leads to the formation of multi-protein complexes at the damaged DNA to link DNA damages to cell cycle arrest (46).

Ataxia-telangiectasia mutated (ATM) protein is a protein kinase which is activated in response to DNA damage. One of the targets of this kinase is the p53-binding protein 1 (53BP1). This protein is characterized by BRCA1 C-terminal domains which are implicated in protein-protein interactions, Tudor domains for the recruitment to the chromatin and a glycine-arginine-rich (GAR) motif which is required for DNA binding. There is ample evidence that 53BP1 contributes to DNA damage repair and suppression of genomic instability (47,48). Knock-down by siRNA experiments revealed that CK2 seems to be necessary for ATM and Chk2 phosphorylation as well as for a 53BP1 foci formation (49). By co- immunoprecipitation experiments it was further shown that CK2 bound to 53BP1 through

its GAR and Tudor domains. This complex formation is impaired in the presence of DNA damage.

A more direct role of CK2 in DNA repair was found when the human DNA repair protein apurinic/apyrimidinic endonuclease (APE) was identified as a CK2 substrate (50). It was shown that phosphorylation of APE by CK2 resulted in a total inactivation of the APE activity. A direct link to p53 was detected when it was shown that APE converts inactive p53 into an active form (51). In a later report, phosphorylation of APE by CK2 was confirmed, however, there was no difference in APE endonuclease activity for CK2 phosphorylated APE (52). Instead, the authors found that the association between the transcription factor AP-1 and APE was inhibited when APE had been phosphorylated by CK2. Based on experiments with an inhibitor of the CK2 kinase activity, namely quercetin, the authors speculated that inhibition of the CK2 phosphorylation of APE might contribute to an increased sensitivity to DNA damage.

It is known for quite some time, that the tumour suppressor gene product BRCA1 participates in DNA repair (53). BRCA1 gets phosphorylated after UV treatment of normal keratinocytes in a dose-dependent manner. Bicyclic monoterpene diols (BMT diols) to some extent can mimic UV treatment of cells. Thus, it was shown that the BMT diol 2,2-dimethyl-3-propanyldiol-norbonane induced phosphorylation of BRCA1 and stimulated the repair of UV-induced pyrimidine dimers (54). Since it was already shown that BRCA1 is a substrate for CK2 (55) inhibition experiments of CK2 with DRB (5,6-dichloro-1-beta-D-ribofuranosylbenzimidazole) (56) revealed a complete inhibition of BRCA1 phosphorylation (54). This inhibition of the BRCA1 phosphorylation is accompanied by an inhibition of the BMT diol stimulated repair of thymidine dimers.

Rad52 from yeast and mammals are key components of DNA double-strand break repair. Sumoylation of Rad52 is induced by DNA damage. This post-translational modification regulated Rad52 stability and activity (57). Rad52 specifically interacted with PTEN and this interaction in particular in the nucleus was enhanced after DNA damage (58) as detected by co-immunoprecipitation experiments as well as by co-immunofluorescence studies. Furthermore, CK2 phosphorylation of PTEN led to nuclear translocation of PTEN where it interacted with Rad52 thereby regulating the sumoylation of Rad52 (58). In eukaryotes Rad51 together with Rad52 and Rad54 catalysed strand transfer between the damaged sequences and its undamaged homologue to allow re-synthesis of the damaged region.

CK2 and mismatch repair

Cells are in constant need for an efficient DNA repair, because up to 10^4 spontaneous depurinations take place in one single cell per day (59). One of the repair mechanisms is mismatch repair, which plays an important role in the maintenance of genomic stability by removal of mispaired nucleotides from DNA. Both mismatch binding proteins MSH2 and MSH6, which form the MutSα complex, are substrates for protein kinase CK2 (*Figure 2*). Inhibition of CK2 by quercetin resulted in a reduced binding of MSH2/MSH6 to mismatches. This result was confirmed by dephosphorylation experiment for MSH2/MSH6 thus providing the first indication for a role of CK2 in mismatch repair (21).

The nucleotide analogue 6-thioguanine is used as an efficient drug in the chemotherapy of a variety of tumours (60). This nucleotide analogue is incorporated into DNA which may later result in an increase in DNA single strand breaks. Incorporation of 6-thioguanine also induces mismatch repair. Following treatment of HeLa cells with 6-thioguanine, CK2α re-localized from the nucleus to the endoplasmic reticulum. No re-localization was found for CK2α' (45). Further evidence for a role of CK2 in mismatch repair stems from experiments which showed that *in vitro* phosphorylation of cell extracts by CK2 increased the cleavage of 8-oxoguanine oligonucleotide considerably (61). 8-Oxoguanine is generated by oxidative stress. It readily forms mismatches with cytosine or adenine. Mutγ is responsible for the repair of 8-oxoguanine. It was not clear, however, whether CK2 phosphorylation of Mutγ is directly implicated in DNA repair or whether it regulates intracellular localization or protein-protein interaction with other repair proteins.

CK2 and nucleotide excision repair

Nucleotide excision repair (NER) is one of the most versatile mammalian DNA repair mechanisms. The transcription factor TFIIH complex Xeroderma pigmentosum group B (XPB) helicase subunit not only functions in transcription but also in NER. XPB was phosphorylated by CK2 in the C-terminus (62). This phosphorylation led to an impaired NER whereas the helicase activity of XPB was not affected. The explanation for this observation might be that CK2 phosphorylation of XPB regulates the recruitment or positioning of other

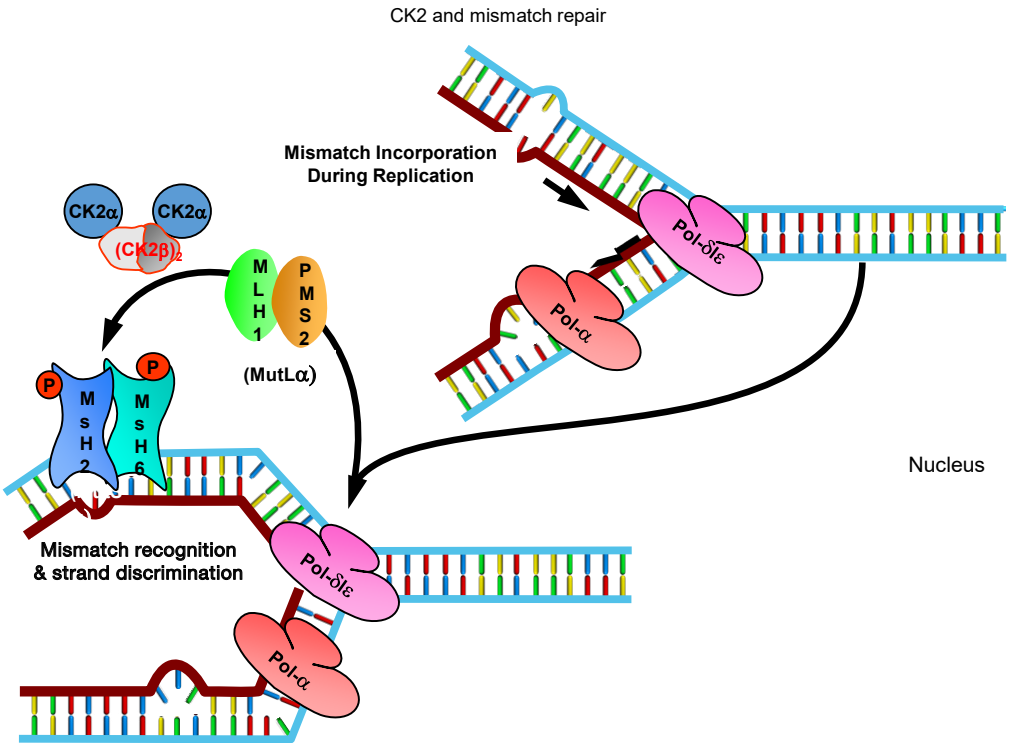

Figure 2 CK2 and mismatch repair. Mismatches are recognized by MsH1/MsH6 which are substrates of CK2.

factors which are inevitable for DNA repair. Some years ago it was shown that another component of the TFIIH complex namely cyclin H is a substrate for CK2 (63) and CK2 phosphorylation regulates cyclin H/cdk7/Mat1 activity. Thus, at least two components of the NER TFIIH complex are CK2 substrates.

Centrins are Ca^{2+} binding proteins, which interact with the Xeroderma pigmentosum group C (XPC) protein, which is also implicated in nucleotide excision repair (64). Phosphorylation of centrins by CK2 regulated binding to G-proteins (65) in a light dependent fashion. CK2 phosphorylation of centrin1 weakly reduced its binding to XPC whereas CK2 phosphorylation of centrin2 reduced binding to XPC considerably (66). The molecular consequences of this reduced binding of centrin2 to XPC remains to be elucidated.

CK2 and non-homologous end joining and homologous recombination

XRCC1 dependent processes

The X-ray repair cross-complementing group 1 (XRCC1) is a member of a family of XRCC proteins which play important roles in these types of DNA repair (67). XRCC1 deficient cells show an accumulation of DNA single-strand breaks after DNA damage and elevated levels of chromosomal aberrations. XRCC1 binds directly to DNA single-strand breaks and gaps in DNA. Since no enzymatic activity was found for XRCC1 it was suggested that XRCC1 is a platform for the binding of other proteins at places of DNA damage.

XRCC1 is directly implicated in the repair of DNA single-strand breaks after exposure of DNA to ionizing radiation or alkylating agents. It interacts with poly (ADP-ribose) polymerase (PARP) and DNA ligase to participate in base excision repair and homologous recombination (68) (*Figure 3*). In the presence of CK2 the DNA ligase I activity was reduced in a CK2 dose-dependent manner (69). This might be due to the phosphorylation of DNA ligase I at serine 66 (35,70). Since DNA ligase I participates in homologous DNA repair and nucleotide excision repair these data support the idea about the important role of CK2 in DNA damage repair. Phosphorylation of XRCC1 by CK2 led to an elevated stability of DNA ligase III (71). XRCC1

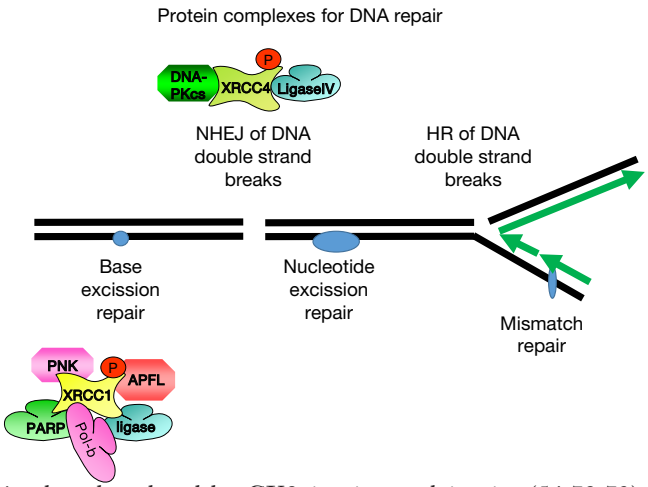

Figure 3 XRCC1 as a CK2 substrate acts as a platform protein for other proteins implicated in base excision repair, NHEJ and HR. IWA functions as an inhibitor of CK2. XRCC1, X-ray repair cross-complementing group 1.

is phosphorylated by CK2 *in vitro* and *in vivo* (54,72,73).

These initial findings were recently extended by the observation that the CK2 phosphorylated XRCC1 interacts with different regions of the fork head associated domain of PNK while the non-phosphorylated XRCC1 binds to the catalytic domain of PNK with lower affinity (50,61,73). Human polynucleotide kinase (PNK) is a DNA repair enzyme which modifies DNA termini to prepare them for DNA repair. It was shown that CK2 phosphorylation of XRCC1 is required for the assembly of XRCC1 into foci at DNA strand breaks together with PNK (73). A role for CK2 in the phosphorylation of XRCC1 was also demonstrated by studies with a CK2 inhibitor (54) and by siRNA knock-down experiments (74). It was recently demonstrated that the cytoplasmic variant of CK2 phosphorylated XRCC1 (71) and this phosphorylation inhibited ubiquitination and proteasomal degradation of XRCC1 as shown by siRNA knock-down of CK2α and CK2α' as well as by mutation of the CK2 phosphorylation sites on XRCC1.

Aprataxin is a protein with some homology to PNK which also plays a role in DNA repair by binding to XRCC1 (53,54). Aprataxin only binds to CK2 phosphorylated XRCC1. Furthermore, binding of aprataxin to XRCC1 was shown to be essential for maintaining the steady-state level of XRCC1. In addition to PNK and aprataxin a third protein denoted aprataxin—and PNK-like factor (APLF) which is also known as Xip1 or PALF (38) were found to bind to XRCC1 and X-ray repair cross-complementing protein 4 (XRCC4) in a CK2 phosphorylation-dependent manner (69). Depletion of APLF is associated with impaired non-homologous end joining (NHEJ) (75). APLF possesses endonuclease and 3'-5' exonuclease activities, it accumulates at sites of single-strand breaks or double-strand breaks where it seems to act as a DNA end-processor. Binding of XRCC1 to APLF seems to be necessary for the regulation of the steady state of APLF. The importance of APLF for DNA damage recognition was demonstrated by depletion experiments which led to a significantly reduced survival in response to single-strand breaks. These results suggest that XRCC1 can recruit one of the three different factors depending on the type of DNA damage. Altogether, phosphorylation of XRCC proteins by CK2 generates a platform on the XRCC1 polypeptide chain where a number of different proteins with functions in DNA damage recognition and repair can bind to.

It was further shown that the phosphorylation of XRCC1 by CK2 was responsible for the translocation of XRCC1 to the nuclear matrix upon oxidative DNA damage by H_2O_2 (76). Thus, another possible role for CK2 might be the direction of repair proteins to places of rapid DNA repair response.

As mentioned earlier, phosphorylation of XRCC1 by CK2 is known to stimulate the repair of single-strand breaks (71,73). Expression of a variant of XRCC1 which cannot be phosphorylated by CK2 leads to low single-strand breaks after treating the cells with the alkylating agent dimethyl sulfate whereas XRCC1 deficient cells displayed elevated levels of single-strand breaks. This reduction in the amount of single-strand breaks was also obtained by using the CK2 specific inhibitor 4,5,6,7-tetrabromo-1H-benzimidazole (DMAT) (77). The reduction of single-strand breaks in the presence of the mutant XRCC1^{ckm} is accompanied by fewer RAD51 foci following dimethyl sulfate treatment of XRCC1^{ckm} cells. Interestingly, most of the non-CK2 phosphorylatable XRCC1^{ckm} was found in a chromatin bound fraction whereas only 25% were found in the soluble fraction.

Induction of DNA damages is a versatile strategy for the treatment of cancers in humans. One of the commonly used cytostatic drugs for the treatment of cancer is cisplatin which induces DNA damage through crosslinking of DNA. XRCC1 was found to bind to such cisplatin induced crosslinks (78). It was recently shown that the selective CK2 inhibitor CX-4945, which is in stage II clinical trials, blocks DNA repair after cisplatin or gemcitabine induced DNA damages. This block in DNA repair is due to an inactivation

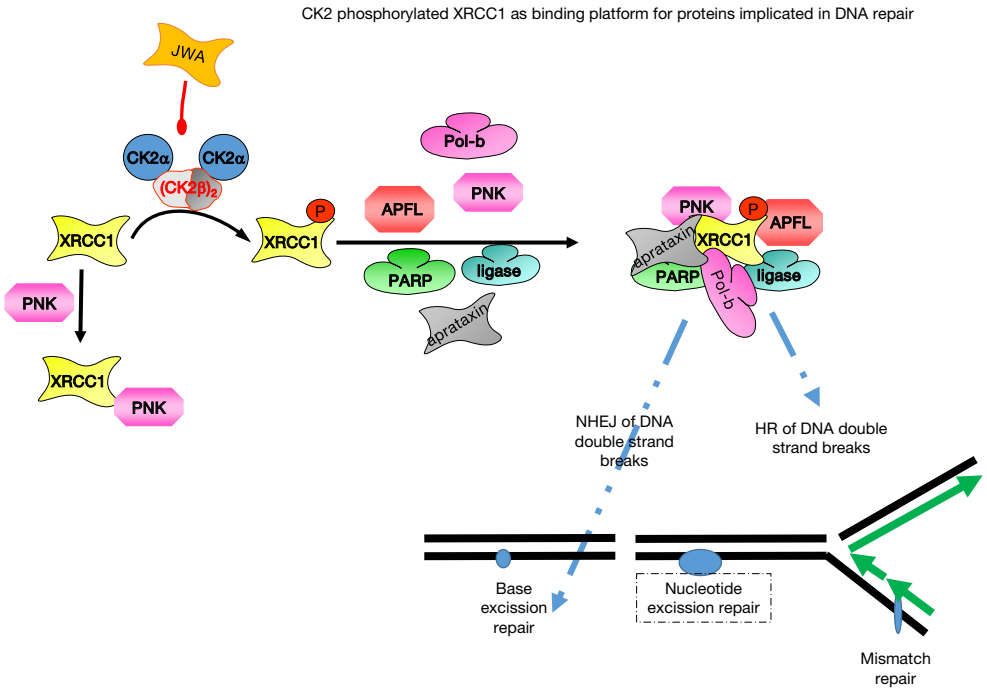

Figure 4 The CK2 phosphorylated XRCC1 and XRCC4 proteins as binding platform for proteins implicated in DNA repair. XRCC1, X-ray repair cross-complementing group 1; XRCC4, X-ray repair cross-complementing protein 4.

of XRCC1 and MDC1 (79,80). These data support the idea that CK2 inhibition is a strategy for a combination therapy of cancer treatment.

JWA is a growth suppressor with multiple functions in cellular responses to oxidative stress and base excision repair as well as melanoma cell adhesion, invasion and metastasis (81-83). A recent study provided data showing that JWA negatively regulated XRCC1 in cisplatin-resistant cells (*Figure 3*). It enhanced cisplatin induced cell death by upregulation of XRCC1 in cisplatin-sensitive cells (80). It was further shown that overexpression of JWA inhibits the CK2 mediated phosphorylation of XRCC1 which is supported by the fact that mutation of the CK2 phosphorylation residues on XRCC1 blocks the negative regulation of JWA on XRCC1.

XRCC4 dependent processes

Very similar observations to XRCC1 were described for the XRCC4, which is one of the several proteins involved in the non-homologous end joining (NHEJ) pathway to repair DNA double strand breaks (DSBs) (*Figure 4*). XRCC4 is a substrate for CK2 and CK2 phosphorylation of XRCC4 is necessary for its interaction with PNK. This interaction is important for DNA double-strand break repair (61) demonstrating that CK2 regulates not only single-strand break repair but also double-strand break repair. In both cases the scaffold proteins XRCC1 and XRCC4 are the link between DNA binding and protein-protein interaction between XRCCs and various proteins. These interactions ensure that DNA end processing and DNA ligation are coordinated. XRCC4 directly interacts with DNA ligase IV, thereby stimulating the ligase activity (84). The XRCC4/DNA ligase IV complex is recruited to DNA double-strand breaks by the DNA dependent kinase (DNA-PK).

Ku70/Ku80/DNA-PK dependent processes

XRCC5 also known as Ku80 and XRCC6 known as Ku70 are components of the DNA-dependent protein kinase complex (DNA-PK) where XRCC7 represents the catalytic subunit of DNA-PK (known as DNA-PK$_{cs}$). The Ku80 and Ku70 proteins form heterodimers which bind to DNA ends acting as a sensor for DNA damage. In non-homologous end joining (NHEJ) DNA-PK plays a role in the detection of DNA double-strand breaks and in the ligation of the DNA ends. Binding of Ku-proteins to double-strand breaks serves to recruit the catalytic subunits of DNA-

dependent protein kinase (DNA-PKcs, ligases and DNA polymerase (85). DNA-PK is a multiply phosphorylated protein. Down-regulation of CK2 subunits by siRNA experiments affected the activity and auto phosphorylation status of DNA-PK which resulted in an inhibition of DNA-PK dependent DNA double-strand break repair. No phosphorylation of DNA-PK by CK2 was shown, however, a proximity ligation assay clearly revealed an interaction of CK2 subunits with DNA-PK. Moreover, as shown by co-immunoprecipitation experiments CK2α and CK2α' bound to DNA-PKcs whereas no binding was found for CK2 and Ku80. Down-regulation of CK2α and CK2α' led to a decrease in the auto-phosphorylation of DNA-PKcs (86). Further experiments showed that the CK2 kinase activity seems to be dispensable for the DNA-PKcs auto-phosphorylation (23). The association between DNA-PKcs and CK2 increased upon induction of DNA strand breaks. In summary a lack of CK2α and CK2α' leads to persistent DNA damage and finally to a reduced survival rate in cells treated with a radiomimetic compound. Probably this interaction is necessary for the phosphorylation of Ku by CK2 (86).

It is an interesting observation that a lack of DNA-PKcs was shown to be accompanied by an increase in the mRNA and protein level for CK2α' but not for the other CK2 subunits. It was further shown that there was no DNA amplification for CK2α' (87) indicating that DNA-PKcs regulated the expression of CK2α'.

Both Ku70 and Ku80 bind to inositol hexakisphosphate (IP_6) and this interaction seems to be necessary for NHEJ. Biotinylated IP_6 was used to precipitate IP_6 binding proteins. This approach demonstrated CK2 as one of the IP_6 binding proteins, which is in agreement with earlier results showing that CK2 bound to IP_6. It was also shown that IP_6 regulates CK2 activity by replacing the CK2 inhibitor NOPP140 from CK2. With these results IP_6 was identified as an activator of CK2 (88,89). One might speculate that the Ku70/Ku80 associated IP_6 modulates the activity of CK2 for NHEJ.

Mre11-Rad50-Nbs1 dependent processes

The Mre11-Rad50-Nbs1 complex also known as MRN complex has emerged as one of the main complexes for homologous recombination as well as for non-homologous end joining. The MRN complex provides the platform for the detection of DNA breaks, it activates DNA repair mechanisms and processes DNA ends for the final ligation process. On the other hand the MRN complex activates the ATM kinase thus linking DNA repair to cell cycle regulation (90). Similar to Mre11, a member of the ABC superfamily of ATPases, Nbs1 forms a dimer within the MRN complex. A function of Nbs1 seems to be the binding platform for a number of different proteins such as CtIP, MDC1, ATR and WRN. It turned out that MDC1 is phosphorylated by CK2 and this phosphorylation seems to be required for its interaction with the MRN complex (91,92) and for the accumulation at DNA double-strand breaks (*Figure 5*). The MDC1 interaction with the MRN complex resembles the interaction previously shown for XRCCs and PNK, aprataxin or APLF. Although the interaction between XRCCs and PNK, aprataxin or APLF is sensitive to pharmacological inhibition of CK2 the MRN-MDC1 interaction is mostly unaffected. A step forward in understanding how the MRN complex and in particular Nbs1 within the MRN complex contributes to DNA repair came from the identification of TCOF1, a nuclear factor, which transiently co-localizes with Nbs1 in the nucleolus rom after DNA damage. Experiments with siRNAs for CK2α and CK2α' revealed that these two subunits were required for the recruitment of Nbs1 to the nucleolus. TCOF1 was phosphorylated by CK2 (93) and it was proposed that MDC1 and TCOF1 interact with Nbs1 in a similar manner through the binding of CK2 sites to Nbs1. This assumption would mean that binding of TCOF1 and MDC1 to Nbs1 is mutually exclusive.

The N-terminus of MDC1 contains many putative CK2 phosphorylation sites. Among these various sites are at least six SDTD motifs within an acidic environment. Interestingly, Nbs1 interacts only with doubly phosphorylated SDTD motifs (22,92). Aprataxin is known to be defective in the neurodegenerative disorder ataxia oculomotor apraxia type 1. This protein binds to sites of DNA damage by an interaction with CK2 phosphorylated SDTD motifs on the polypeptide chain of MDC1 (94). Mutational analysis, however, revealed that CK2 phosphorylation is not the sole factor required for this interaction because mutation of arginine 29 disrupted the interaction between aprataxin and MDC1. Further experiments have shown that MDC1 is not necessary for the recruitment of aprataxin to sites of DNA strand breaks but rather MDC1 seems to be a platform for aprataxin and probably other proteins to ensure an effective DNA repair. Interestingly, CK2 seems not to be located at sites of DNA damage, which means that CK2 phosphorylation occurs before the association of these proteins with damaged DNA.

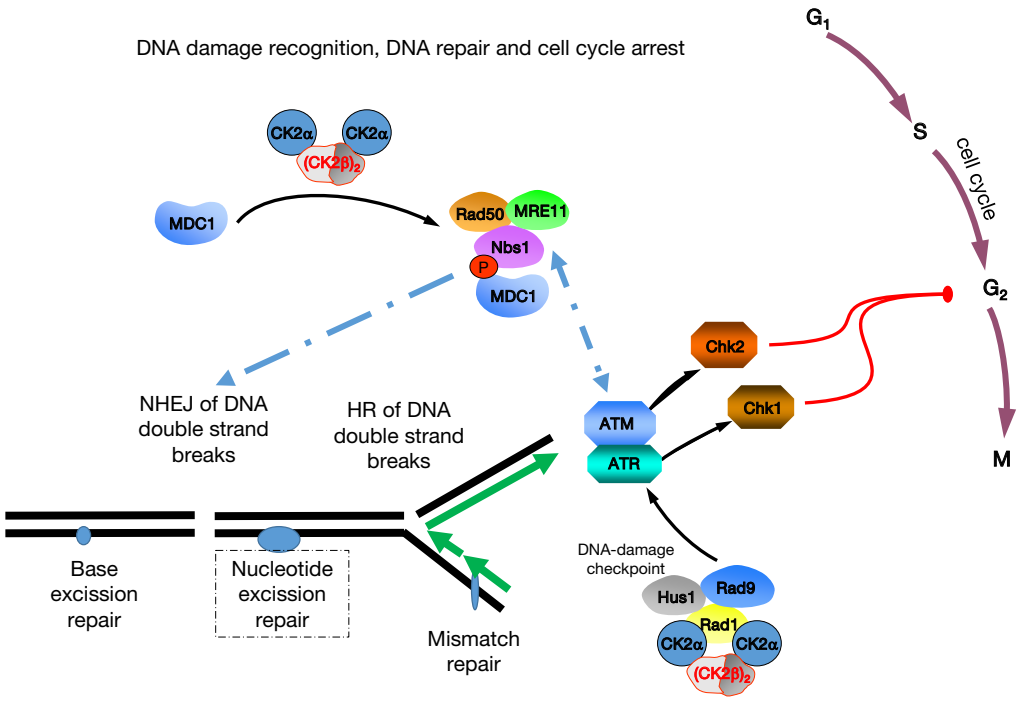

Figure 5 The link between DNA damage recognition, DNA repair and cellular signalling leading to cell cycle arrest in the G2-phase of the cell cycle.

In Schizosaccharomyces pombe the Mre11-Rad50-Nbs1 complex also plays an important role in homologous recombination. The Ctp1 protein cooperates in this process and it is recruited to DNA single strand breaks by interacting with the MRN complex. CK2 phosphorylated SDTD motifs serve as the preferred docking sites for Ctp1/Nbs1 binding. Thus, it has been shown that the CK2 phosphorylation dependent protein-protein interaction not only plays a role in non-homologous end joining (NHEJ), single-strand break repair but also in homologous repair (53,75,95).

One other factor which is implicated in NHEJ is the Rad51 recombinase, which catalyses homologous pairing and strand exchange during homologous recombination. Recruitment and activity of Rad51 is among others stimulated by BRCA2. Rad51 is phosphorylated by CK2. This phosphorylation is primed by a previous phosphorylation by polo like kinase 1 (Plk1). It was further shown that the combined phosphorylation of Rad51 by Plk1 and CK2 triggers its interaction with Nbs1. CK2 phosphorylation of Rad51 is important for the co-ordination of precise recombination events at the DNA (96).

Besides the MRN complex, MDC1 and 53BP1, the MDC1 dependent recruitment of E3 ligase RNF8-RNF168 facilitates DNA strand break signalling and DNA repair. The recruitment of 53BP1 to DNA damage sites seems to depend on two histone modification such as methylation of H4K20 and ubiquitination of H2AK15. RNF168 is required for the recruitment of the lysine-specific demethylase LSD1 to sites of DNA damage. By co-immunoprecipitation assays and by pull-down assays it was shown that LSD1 bound to CK2α' and to a lesser extent to CK2α. In addition LSD1 was phosphorylated by CK2α' (97). This is one of the very few reports indicating a specific role of CK2α'.

Miscellaneous CK2/protein interactions

TopBP1 is a multifunctional protein, which is has been identified as a binding partner of DNA topoisomerase II (98,99). Later on, a member of the TopBP family of proteins, namely TopBP1, turned out to be a scaffold for numerous protein-protein interactions through BRCT (BRCA1 C-terminus) domains. TopBP1 binds to sites of DNA damage and to Rad9 within the Rad9-Hus1-Rad1 (9-1-1) checkpoint clamp. Moreover, serine 387 of Rad9 which is required for its interaction with TopBP1 is phosphorylated

by CK2 (100). In addition TopBP1 stimulates the kinase activity of ATR. Thus, the CK2 substrate TopBP1 seems to be the link between DNA repair and cell cycle regulation. In the same year Takeishi *et al*., reported that in addition to serine 387 also serine 341 was phosphorylated by CK2 at least *in vitro* (101). TopBP1 bridges the 9-1-1 checkpoint clamp and the ATM-ATR interacting protein which are recruited independently onto damaged chromatin. Recently, it was shown that the recruitment of Rad9 to UV-damaged DNA is independent of its binding to TopBP1 (102). The Rad9-Hus1-Rad1 complex is a heterotrimer which is loaded onto damaged chromatin (103). It was demonstrated that CK2 phosphorylates Rad9 within the C-terminal tail (101). The phosphorylated serine residue 387 has been shown to be important for binding to TopBP1. It turned out that in addition to serine 387 also CK2 phosphorylation at residue 341 seems to be important for DNA damage response in human cells. Phosphorylation at these sites are not DNA-damage dependent. This observations seems to be very similar to a previous result with MDC1 which is also constitutively phosphorylated by CK2 and the interaction between MDC1 and Nbs1 takes place in the absence of DNA damage (91,92). Furthermore, by tandem mass spectrometry and by co-immunoprecipitation experiments it was shown that CK2α, CK2α' and CK2β interacted with the Rad9-Hus1-Rad1 complex (*Figure 5*).

Shortly after ionizing radiation of malignant glioma cells the catalytic activity of CK2 increased and this activity was inhibited by apigenin (104) a flavonoid, which was used in a clinical phase II study for the treatment of colorectal cancer (NCT 00609310). It was reported that UV treatment of tumour cells resulted in enhanced expression of CK2α (105,106). It turned out that CK2 knock-down in the malignant glioma cells did not inhibit DNA double strand break repair (104). It was further shown that apigenin increased the radiation induced phosphorylation of CK2, which is a target of DNA-PK (107). CK2 inhibition by apigenin did not radio-sensitize the two tested glioma cell lines. Inhibition of CK2 by tetrabromobenzotriazole (TBB) or down-regulation of CK2 by siRNA experiments increased apoptosis in human lung cancer cells, which is accompanied by elevated cytochrome C release from mitochondria and by cleaved caspase 3.

HspA1A also known as Hsp70 is a member of the family of inducible heat shock proteins in mammalian cells, which protects cells against DNA damage (108). HSPA1A binds to apurinic/apyrimidinic endonucleases (109) to stimulate endonuclease activity. It binds to XRCC1 (109) and it enhances base excision repair after ionizing radiation (110). Recently, by co-immunoprecipitation it was found that HSPA1A bound to CK2 (111) and this interaction increased after treatment of the cell with the DNA damaging agent benzo[a]pyrene. Con-focal immunofluorescence microscopy revealed that HSPA1A and CK2 co-localized in the cell nucleus and perinuclear. Furthermore, it was shown that overexpression of HSPA1A resulted in an enhanced CK2 kinase activity. It might well be that the interaction between HSPA1A and CK2 targets CK2 to sites of DNA damage where CK2 is activated by HSPA1A to phosphorylate XRCC1 or DNA-PK.

Another protein which is implicated in DNA damage repair is OTUB1 which is a member of isopeptidases, which remove ubiquitin chains form proteins (112,113). It was recently shown that CK2α phosphorylates OTUB1 *in vitro* and *in vivo*. Further experiments revealed that OTUB1 belongs to CK2 substrates, which are phosphorylated by the catalytic CK2α subunit alone as well as by the CK2 holoenzyme. CK2 phosphorylation of OTUB1 at serine 16 promotes nuclear localisation of OTUB1 (114). Furthermore, CK2 phosphorylation of OTUB1 seems to be necessary for the repair of IR induced DNA damage. The precise role of OTUB1 in DNA repair, however, is not resolved.

Concluding remarks and perspectives

Protein kinase CK2 is a multifunctional enzyme which plays a role in diverse cellular processes. Here, I have added functions of CK2 in DNA damage recognition and repair and down-stream signalling. Early reports on CK2 in this context pointed already to a role of CK2 in the regulation of the chromatin structure, which was evident by the CK2 phosphorylation of histones. One of the key molecules in sensing DNA damage, induction of cell cycle arrest and DNA repair is p53, which was detected as a CK2 substrates in the early 90 of the last century. Components of the transcription factor complex TFIIH, which is also known to be implicated in DNA repair, were also identified as CK2 substrates (*Table 1*). In the course of these studies there were the first indications that CK2 not only phosphorylated various substrates in the context of DNA damage and repair but individual subunits of CK2 or the holoenzyme bound to cellular proteins where the functional consequences of this binding remains to be elucidated. Binding of CK2 to various proteins might in many cases reflect an enzyme/substrate interaction. There is, however, also the possibility

Table 1 Substrates of protein kinase CK2 which are implicated in DNA damage recognition, -repair or down-stream signalling

Protein	Reference
p53	(29,30-32)
Apurinic/pyrimidinic endonuclease (APE)	(51,52)
Mismatch binding protein MS42	(21)
Mismatch binding protein MS46	
DNA ligase I	(35,70)
BRCA1	(55)
Cyclin H	(63)
XPB	(62)
XRCC1	(50,61,72,73)
XRCC4	(75)
histone H1	(22)
MDC1	(91,92)
Rad51	(96)
TopBP1	(100)
Rad9	(101)
OTUB1	(114)

XPB, xeroderma pigmentosum group B; XRCC1, X-ray repair cross-complementing group 1; XRCC4, X-ray repair cross-complementing protein 4.

that CK2 is targeted to specific substrates by binding to transport proteins.

CK2 also links DNA damage recognition to cell cycle arrest, which gives the cell time for DNA repair. This is mostly evident by the observation that CK2 seems to be necessary for p53, $p21^{WAF1}$, ATM, ATR, Chk2 and cdk1 phosphorylation.

CK2 is implicated in the phosphorylation of proteins, which are central in mismatch repair, nucleotide excision repair, homologous recombination and non-homologous end joining. Interestingly CK2 phosphorylates proteins such as XRCC1, XRCC4 and MDC1, which are platform proteins for the recruitment of other proteins to the damaged DNA for repair. CK2 phosphorylation of these proteins regulates binding of these proteins to the platform proteins.

Over the last 10 years a number of inhibitors of the kinase activity have been developed and a few of them are in clinical phase I or II trials. On the other hand, the induction of DNA damage by various cytostatic is a strategy for the treatment of cancer. Actually there are a few studies coming up where combinations of CK2 inhibitors and well known DNA damage inducing cytostatic have been used for the treatment of cancer with promising results. These initial results open a wide field for future research about CK2 in clinical trials.

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Footnote

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.3978/j.issn.2218-676X.2016.01.09). The author has no conflicts of interest to declare.

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