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The Involvement of E2F1 in the Regulation of XRCC1-Dependent Base Excision DNA Repair

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1. Introduction

Reactive oxygen species, ionizing radiation and alkylating agents can attack on DNA resulting in single or double strand breaks, generation of abasic sites, base and sugar lesions [1]. Double-strand breaks (ds breaks) are repaired by two different types of mechanism. One type takes advantage of proteins that promote homologous recombination (HR) to obtain instructions from the sister or homologous chromosome for proper repair of breaks. The other type permits joining of ends even if there is no sequence similarity between them. The latter process is called non-homologous end joining (NHEJ).The process by which complex single-strand breaks (those that cannot be directly religated) are repaired (SSBR) in some ways resembles NHEJ. Here we shall mainly discuss the mechanism of base excision repair (BER) of SSBR.

2. Base excision DNA repair

The major pathway to remove damaged DNA bases is Base Excision Repair (BER, *Fig. 1*). BER can be divided into five steps: (i) excision of damaged base by the specific DNA glycosylase and formation of apurinic/apyrimidinic (AP) site; (ii) cleavage of phosphodiester bond at AP site by AP-endonuclease or AP-lyase; (iii) removal of chemical groups interfering with gap filling and ligation; (iv) gap filling; (v) ligation [2].
The first step of the BER pathway is recognition of damaged base by the specific DNA glycosylase, which cleaves N-glycosidic bond leaving behind a free base and an AP site. In humans about 10 DNA glycosylases of different, but partially overlapping substrate specificities are known [3]. Some of them are bifunctional enzymes, which have endowed AP-lyase activity and cleave phosphodiester bonds at 3′ side of AP site either by ß- or ß/δ -elimination. *E. coli* endonuclease III (Nth), its human homolog, hNTH1 and human 8-oxoG DNA glycosylase (OGG1) catalyse reaction of ß- elimination, which creates alpha/ß-unsaturated aldehyde (3′dRP) at the 3′ end of cleaved DNA strand. Bacterial formamidopyrimidine DNA glycosylase (Fpg), endonuclease VIII (Nei) and two human homologs of the latter, NEIL1 and NEIL2 catalyse ß/ δ-elimination and remove deoxyribose residue leaving phosphate at the 3′ end of cleaved DNA strand. Monofunctional DNA glycosylases need the assistance of AP-endonucleases, which hydrolyse phosphodiester bond at the 5′ end of the AP site. This yields DNA single strand break (SSB) with the 5′end

bearing baseless deoxyribose (5′dRP) and the 3′ end with the free hydroxyl group. Both AP sites and SSBs can be formed due to spontaneous hydrolysis of purines, as well as upon DNA damaging agents, like ionizing radiation or oxidation.

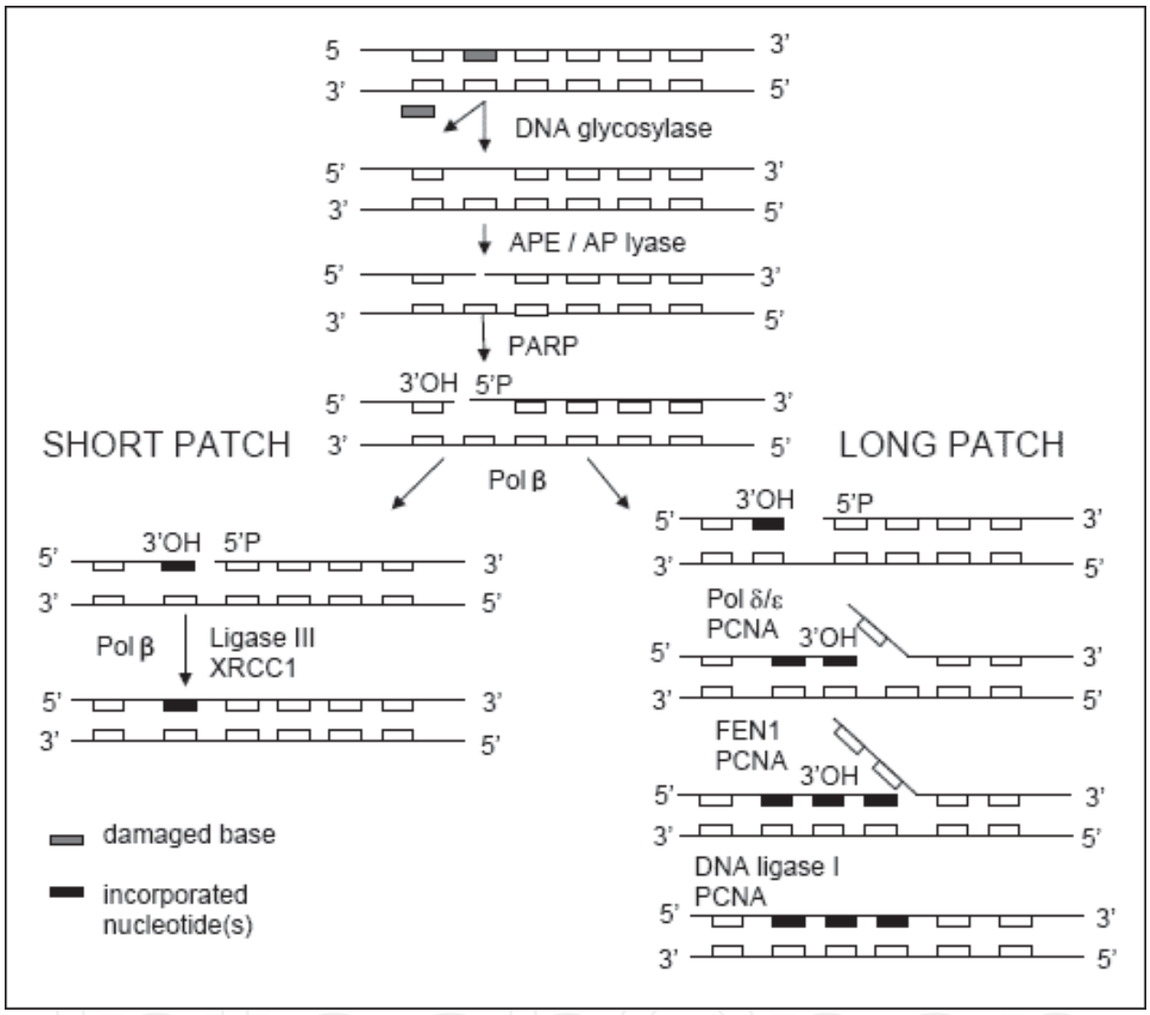


Fig. 1. Base Excision Repair pathway

Before filling the gap by DNA polymerases possible additional chemical groups present on 3′OH end, which may block polymerisation, must be removed. Bacterial enzymes Xth (exonuclease III) and Nfo (Endonuclease IV), besides of cleaving phosphodiester bonds at 5′ AP-site, have as well 3′ phosphatase and 3′ phosphodiesterase activities and remove phosphates and phosphoglycolates from 3′ hydroxyl group of cleaved DNA strand[4]. In contrast, the major mammalian AP-endonuclease, APE1 effciently removes 3′ phosphoglycolate groups, but has a very weak 3′ phosphatase activity [5]. Phosphate groups left e.g. by NEIL1 glycosylase at 3′hydroxyls are most probably removed by polynucleotide kinase[6]. After cleavage of phosphodiester bond, repair may be continued on two alternative pathways (*Fig. 1*): *short-patch* BER (SP-BER) or *long patch* BER (LP-BER). During SP-BER in mammals, only one missing nucleotide is incorporated by DNA polymerase ß (pol ß), which has also endowed 5′dRPase activity and can remove baseless sugar from the

5'site of DNA break. In LP-BER a longer fragment ranging from 2 to 12 nucleotides is excised and re-synthesized [2]. Initially DNA polymerase elongates 3' end by a few nucleotides and moves aside a DNA fragment which contains 5' deoxyribophosphate. Subsequently, such flap structure is cleaved out by specific flap endonuclease, FEN1. It is believed that in LP-BER the first nucleotide is incorporated by DNA polymerase ß, while next ones by DNA polymerases δ or ε [2]. LP-BER demands also other assisting proteins, PCNA (*proliferating cell nuclear antigen*) and RPC (*replication protein C*).
The last stage of BER is ligation of repaired DNA fragments by DNA ligase. Different DNA ligases(LIG) are operating in short and long patch BER, LIG1 in LP-BER and LIG3alpha in SP-BER. LIG3alpha remains in complex with XRCC1 (x-ray repair cross-complementing group 1) protein, which activates ligation of DNA ends by LIG3alpha.

3. The role of XRCC1 protein in base excision DNA repair

X-ray cross-complementing group 1 (XRCC1) is a 70- kDa protein comprising three functional domains; an N-terminal DNA binding domain, a centrally located BRCT I and a C-terminal BRCT II domain. It has no known enzymatic activity. Since it specifically interacts with nicked and gapped DNA *in vitro*[7-9], and rapidly and transiently responds to DNA damage in cells, it may serve as a strand-break sensor [10, 11].
DNA single-strand breaks (SSBs) are one of the most frequent types of DNA damage in cells [12]. SSBs can lead to the accumulation of mutations or can be converted from single to cytotoxic double-strand breaks. Thus, SSBs pose a critical threat to the genetic stability and survival of cells[13]. Various proteins have been identified that are part of the repair machinery for SSBs, including XRCC1 protein. XRCC1 has been shown to be critically involved in DNA SSB repair in studies using XRCC1-mutant cells and XRCC1 knockout mice[14], which have increased sensitivity to alkylating agents, ultraviolet and ionizing radiation [15], as well as elevated levels of sister chromatic exchange. Since XRCC1 interacts with many proteins known to be involved in BER and SSBR, it has been proposed that XRCC1 functions as a scaffold protein able to coordinate and facilitate the steps of various DNA repair pathways[11, 16]. For example, XRCC1 interacts with several DNA glycosylases involved in repair of both oxidative and alkylated base lesions, and stimulates their activity[17, 18]. This protein interacts with DNA ligase III, polymerase beta and poly (ADP-ribose) polymerase to participate in the base excision repair pathway. It is recruited to the site of DNA damage by several DNA glycosylases, e.g. OGG1 or NTH1 and remains at the site of repair till the last stage of ligation (*Fig. 2*), regulating and coordinating the whole process. XRCC1 facilitates exchange of DNA glycosylase with AP-endonuclease at the damaged substrate, which increases the excision rate of modified base, regulates pol ß interactions with APE1, and finally activates ligation step [17]. Binding of XRCC1 to Polynucleotide Kinase (PNK) enhances its capacity for damage discrimination, and binding of XRCC1 to DNA enables displacement of PNK from the phosphorylated product [19] thus accelerating SSBR of damaged DNA[20]. XRCC1 associates with Tyrosyl-DNA phosphodiesterase1(Tdp1) and enhances its activity required for repair of Top1-associated SSBs. It may act to recruit Tdp1 to these damaged sites[21]. Biochemical and nuclear magnetic resonance (NMR) experiments have demonstrated protein-protein interaction between the N-terminal domain of XRCC1 and the polymerase domain of pol β[22-25]. Additionally, stabilization of DNA ligase IIIα is dependent on its interaction with the BRCT II domain of XRCC1[26]. Aprataxin also interacts with XRCC1 and functions to maintain

XRCC1 stability, thus further linking the neurological degeneration associated with ataxia to an inefficiency of SSBR[27-29].

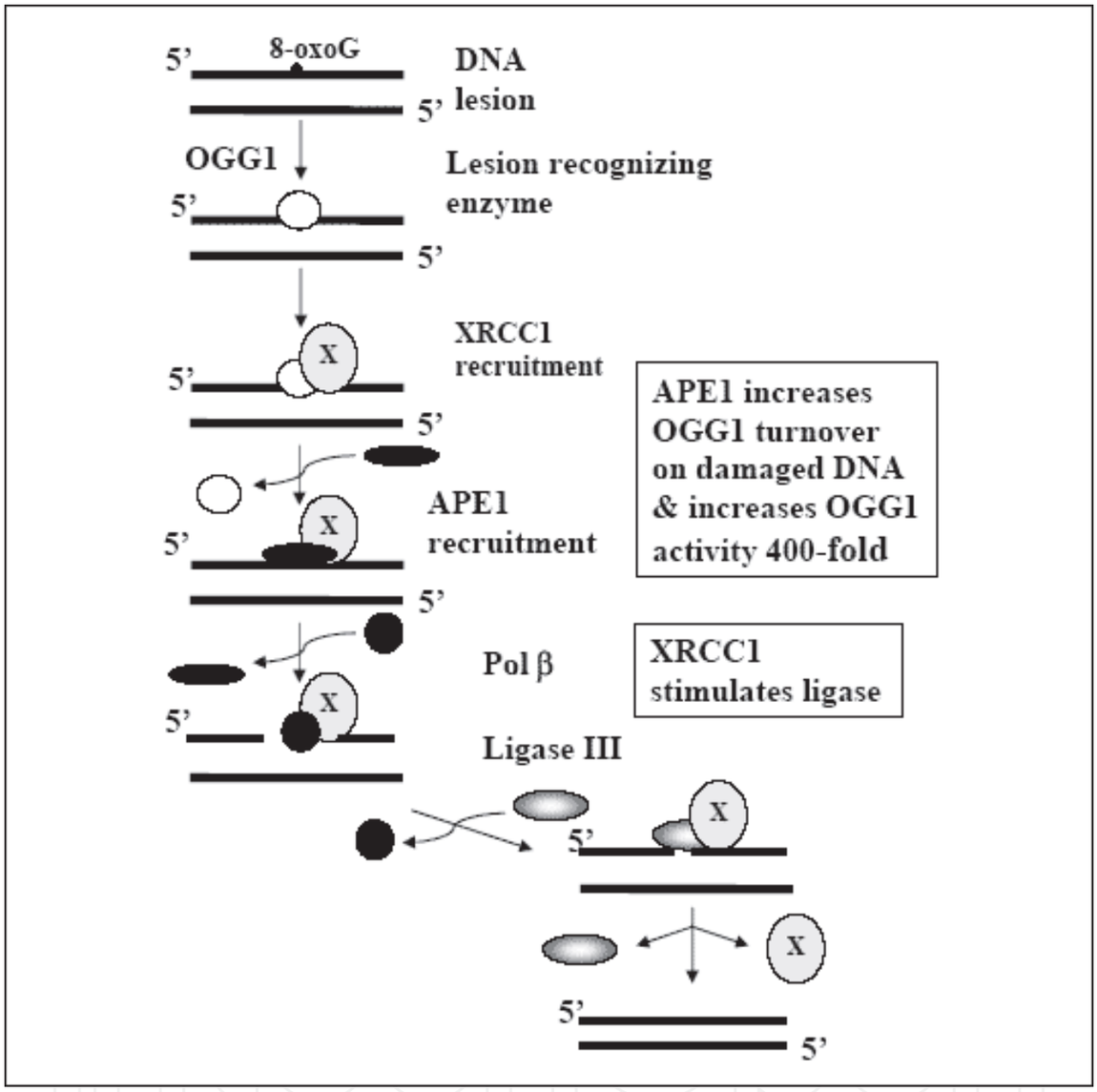


Fig. 2. Coordinative role of XRCC1 protein in BER

Several additional proteins participate in BER and play regulative and coordinative role. The most important proteins are: PARP1 (polyADP ribose polymerase, which binds to free DNA ends and protects them against degradation, participates in chromatin relaxation and probably modulates binding of repair proteins to the site of damage by interaction with poly(ADP-ribose) chains [22, 30, 31], PCNA (proliferating cells nuclear antigen, DNA polymerase processivity subunit in LP-BER), RFC (replication factor C, loading PCNA on DNA), WRN (helicase deficient in Werner syndrome, a premature aging disease) or CSB (helicase deficient in Cockayne syndrome, neurodevelopmental and premature aging disease).

4. The role of E2F1 in XRCC1 associated base excision DNA repair

E2F1 is a member of E2F family of transcription factors which plays an important role in promoting both cellular proliferation and cell death. E2F1 is important for regulating S-phase specific genes as well as promoting apoptosis, just as other "activating" E2F family members [32, 33]. Simultaneously, E2F1 regulates DNA repair through interaction with other factors including RB family proteins, p53 and X-ray repair cross-complementing group 1 (XRCC1) protein.

4.1 E2F family

The E2F transcription factor family consists of at least seven distinct genes divided into two groups. E2F1, E2F2, E2F3, E2F4, and E2F5 constitute one group, while the related DP1 and DP2 genes constitute the other group. Several forms of the DP2 (also referred to as DP3) protein can be produced as the result of alternative splicing, thus providing additional complexity to the E2F family. A functional E2F transcription factor consists of a heterodimer containing an E2F polypeptide and a DP polypeptide. Each of the five E2F polypeptides can heterodimerize with either DP1 or DP2 (DP3). Furthermore, each of these E2F/DP heterodimers (referred to as E2F factors hereafter) can bind consensus E2F sites *in vitro* and stimulate transcription when overexpressed[34].

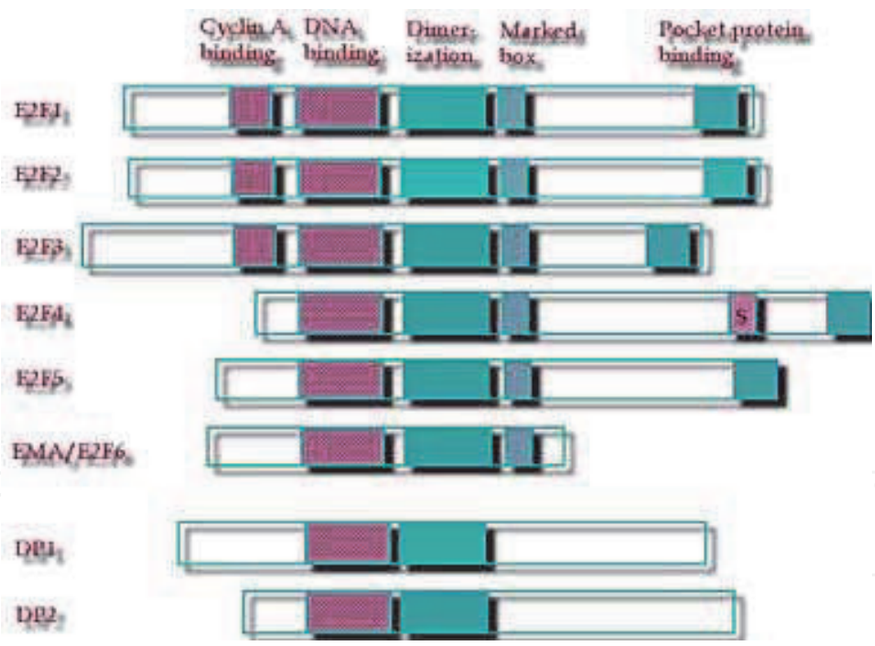


Fig. 3. the members of E2F

All of the E2F subgroup proteins have a similar structure although E2F1, E2F2, and E2F3 are more closely related to each other than to E2F4 and E2F5 (*Fig. 3*). The DNA-binding domain found in the amino terminus represents the area of greatest homology between the five E2F species. Adjacent to the DNA-binding domain is the DP dimerization domain, which contains within it a leucine heptad repeat. The carboxy termini of the five E2F polypeptides contain the defined transcriptional activation domains, which are characterized by an abundance of acidic residues. Embedded within the transactivation domain of each E2F is a

region of homology involved in binding to the pocket proteins (Rb, p107, and p130). An additional region of homology, termed the Marked box, lies between the DP dimerization and transcriptional activation domains. Although this Marked box motif is highly conserved between the different E2Fs, its function is unknown. The amino termini of E2F1, E2F2, and E2F3 contain an additional region of homology not found in E2F4 or E2F5. This region has been demonstrated to have several functions, including binding to the cyclin A protein. The E2F4 protein contains a stretch of consecutive serine residues between the Marked box and the pocket protein binding domain not found in other E2F family members. DP1 and DP2 polypeptides contain DNA-binding and dimerization domains related to the E2F proteins but do not contain transcriptional activation domains or regions homologous to the pocket protein binding or Marked box domains.

An additional E2F family member has recently been isolated and termed EMA (E2F-binding site modulating activity) or E2F6[35, 36]. EMA/E2F6 shares homology with the E2F polypeptides in the DNA-binding domain, the DP dimerization domain and the Marked box, but lacks the pocket protein binding domain and acidic transcriptional activation domain found in the carboxy terminus of the other E2F species (figure 1). Like the other E2F polypeptides, EMA/E2F6 dimerizes with DP1 or DP2 and, in conjunction with a DP partner, binds E2F DNA-binding sites with preference for a subset of sites with the core sequence TCCCGCC. EMA/E2F6 appears to function as a repressor of E2F site-dependent transcription independent of pocket protein binding. The mechanism of repression is either through competitive inhibition with other E2F species or through an active transcriptional repression domain located in the amino terminus of EMA/E2F6.

4.2 E2F factors and Rb family of pocket proteins

The activity of E2F factors is regulated through association with the retinoblastoma tumor suppressor protein (Rb) and the other pocket proteins, p107 and p130. Binding of Rb, p107 or p130 converts E2F factors from transcriptional activators to transcriptional repressors. The interplay among G1 cyclins (D-type cyclins and cyclin E), cyclin-dependent kinases (cdk4, 6, and 2), cdk inhibitors, and protein phosphatases determines the phosphorylation state of the pocket proteins which in turn regulates the ability of the pocket proteins to complex with E2F. E2F activity is further regulated through direct interactions with other factors, such cyclin A, Sp1, p53 and the ubiquitin-proteasome pathway. Deregulated expression of E2F family member genes has been shown to induce both inappropriate S phase entry and apoptosis. Experiments show that dimerization between E2F1 and its partner DP1 is stable and that E2F1 stimulates nuclear localization of DP1[37]. E2F1/DP1 is acetylated by the three acetyltransferases P300/CBP-associated factor (PCAF), cAMP-response element-binding protein (CREBBP) and p300 which stabilizes E2F1 protein[38]. The acetylated complex is able to bind to PCAF to form an active dimer. The complex ability to bind to DNA on the promoter sites of its target genes along with its transcriptional activity are increased at the G1/S transition. During G2, the complex is phosphorylated by CycA2/CDK2[39]. The affinity between E2F1 and DP1 is then diminished leading to the dissociation of the complex and the release of PCAF[40]. The proteins undergo further modifications before degradation: E2F1 is deactelylated by histone deacetylase1(HDAC1) [41], dephosphorylated and phosphorylated *de novo* during S phase by Transcription factor II H (TFIIH) kinase for rapid degradation[42].

Upon DNA damage, the complex PCAF/E2F1/DP1 can be phosphorylated and stabilized either by Checkpoint kinases (CHEK1 and CHEK2) through phosphorylation at Ser-364, or

by ataxia telangiectasia mutated(ATM) and ATR (ATM and Rad3-related) [43, 44], preventing E2F1 ubiquitination[45]. E2F1 mediates the transcription of many genes involved in apoptosis. However, E2F1 transcriptional activity can also be inhibited when bound to the topoisomerase TopBP1 in order to give time to the cell to repair the damage [46]. Mutations of the RB gene represent the most frequent molecular defect in Osteosarcoma. Studies in animal models and in human cancers have shown that deregulated E2F1 overexpression possesses either "oncogenic" or "oncosuppressor" properties, depending on the cellular context. High E2F1 levels exerted a growth-suppressing effect that relied on the integrity of the DNA damage response network. Surprisingly, induction of p73, an established E2F1 target, was also DNA damage response-dependent. Furthermore, a global proteome analysis associated with bioinformatics revealed novel E2F1-regulated genes and potential E2F1-driven signaling networks that could provide useful targets in challenging this aggressive neoplasm by innovative therapies[47]. Similarly, deregulation of the Rb/E2F pathway in human fibroblasts results in an E2F1-mediated apoptosis dependent on ATM, Nijmegen breakage syndrome 1 (NBS1), CHEK2 and p53. E2F1 expression results in MRN(Mre11-Rad50-Nbs10 foci formation, which is independent of the Nbs1 interacting region and the DNA-binding domain of E2F1. E2F1-induced MRN foci are similar to irradiation-induced foci (IRIF) that result from double-strand DNA breaks because they correlate with 53BP1 and gammaH2AX foci, do not form in NBS cells, do form in AT cells and do not correlate with cell cycle entry. In fact, in human fibroblasts, deregulated E2F1 causes a G1 arrest, blocking serum-induced cell cycle progression, in part through an Nbs1/53BP1/p53/p21(WAF1/CIP1) checkpoint pathway. This checkpoint protects against apoptosis because depletion of 53BP1 or p21(WAF1/CIP1) increases both the rate and extent of apoptosis. Nbs1 and p53 contribute to both checkpoint and apoptosis pathways. These results suggest that E2F1-induced foci generate a cell cycle checkpoint that, with sustained E2F1 activity, eventually yields to apoptosis. Uncontrolled proliferation due to Rb/E2F deregulation as well as inactivation of both checkpoint and apoptosis programs would then be required for transformation of normal cells to tumor cells[48]. ZBRK1 is a zinc finger-containing transcriptional repressor that can modulate the expression of GADD45A, a DNA damage response gene, to induce cell cycle arrest in response to DNA damage. Liao et al found that the ZBRK1 promoter contains an authentic E2F-recognition sequence that specifically binds E2F1, but not E2F4 or E2F6, together with chromatin remodeling proteins CtIP and CtBP to form a repression complex that suppresses zinc finger protein (ZBRK1) transcription. Furthermore, loss of RB-mediated transcriptional repression led to an increase in ZBRK1 transcript levels, correlating with increased sensitivity to ultraviolet (UV) and methyl methanesulfonate-induced DNA damage. Thus, the RB.CtIP (CtBP interacting protein)/CtBP (C terminus-binding protein) /E2F1 complex plays a critical role in ZBRK1 transcriptional repression, and loss of this repression may contribute to cellular sensitivity of DNA damage, ultimately leading to carcinogenesis[49]. One study suggested that E2F1 is also a transcriptional regulator of Xeroderma pigmentosum group C(XPC) and Rb/E2F1 tumor suppressor pathway is involved in the regulation of the DNA lesion recognition step of nucleotide excision repair[50]. Disruption of pRB-E2F interactions by E1A is a key event in the adenoviral life cycle that drives expression of early viral transcription and induces cell cycle progression. This function of E1A is complicated by E2F1. pRB-E2F1 interactions are resistant to E1A-mediated disruption. Using mutant forms of pRB that selectively force E2F1 to bind through only one of the two binding sites on pRB, E1A is unable to disrupt E2F1's unique interaction with pRB. Furthermore, analysis of pRB-E2F complexes during

adenoviral infection reveals the selective maintenance of pRB-E2F1 interactions despite the presence of E1A[51].

4.3 E2F1 factors and DNA repair

The E2F1 transcription factor is post-translationally modified and stabilized in response to various forms of DNA damage to regulate the expression of cell cycle and pro-apoptotic genes. E2F1 also forms foci at DNA double-strand breaks (DSBs). The absence of E2F1 leads to spontaneous DNA breaks and impaired recovery following exposure to ionizing radiation. E2F1 deficiency results in defective NBS1 phosphorylation and foci formation in response to DSBs but does not affect NBS1 expression levels. Moreover, an increased association between NBS1 and E2F1 is observed in response to DNA damage, suggesting that E2F1 may promote NBS1 foci formation through a direct or indirect interaction at sites of DNA breaks. E2F1 deficiency also impairs RPA and Rad51 foci formation indicating that E2F1 is important for DNA end resection and the formation of single-stranded DNA at DSBs. These findings establish new roles for E2F1 in the DNA damage response, which may directly contribute to DNA repair and genome maintenance[52]. Chromatin structure is known to be a barrier to DNA repair and a large number of studies have now identified various factors that modify histones and remodel nucleosomes to facilitate repair. In response to ultraviolet (UV) radiation several histones are acetylated and this enhances the repair of DNA photoproducts by the nucleotide excision repair (NER) pathway. The E2F1 transcription factor accumulates at sites of UV-induced DNA damage and directly stimulates NER through a non-transcriptional mechanism. E2F1 associates with the general control nonderepressible(GCN5) acetyltransferase in response to UV radiation and recruits GCN5 to sites of damage. UV radiation induces the acetylation of histone H3 lysine 9 (H3K9) and this requires both GCN5 and E2F1. Moreover, as previously observed for E2F1, knock down of GCN5 results in impaired recruitment of NER factors to sites of damage and inefficient DNA repair. These findings demonstrate a direct role for GCN5 and E2F1 in NER involving H3K9 acetylation and increased accessibility to the NER machinery[53].

Mice lacking E2F1 have increased levels of epidermal apoptosis compared to wild-type mice following exposure to ultraviolet B (UVB) radiation. Moreover, transgenic overexpression of E2F1 in basal layer keratinocytes suppresses apoptosis induced by UVB. Inhibition of UVB-induced apoptosis by E2F1 is unexpected given that most studies have demonstrated a proapoptotic function for E2F1. E2F1-mediated suppression of apoptosis does not involve alterations in mitogen-activated protein kinase activation or B-cell lymphoma (Bcl-2) downregulation in response to UVB and is independent of p53. Instead, inhibition of UVB-induced apoptosis by E2F1 correlates with a stimulation of DNA repair. Mice lacking E2F1 are impaired for the removal of DNA photoproducts, while E2F1 transgenic mice repair UVB-induced DNA damage at an accelerated rate compared to wild-type mice. These findings suggest that E2F1 participates in the response to UVB by promoting DNA repair and suppressing apoptosis[54]. One study showed that E2F1 has a direct, non-transcriptional role in DNA repair involving increased recruitment of NER factors to sites of damage[55].

4.4 The role of E2F1 in the regulation of XRCC1-dependent BER

The exact mechanism of E2F1 regulating XRCC1-dependent base excision DNA repair is still not completely clear. The E2F1 pathway is centrally involved in the highly complex

networks coupling cellular proliferation and apoptosis. XRCC1, which plays a critical role in SSBR/BER [15], is a direct E2F1 target gene. E2F1 is upstream of XRCC1 significantly expands on prior observations that E2F plays a role in other repair pathways, such as MMR and NER [56-59]. The BER protein uracil-DNA glycosylase is also E2F-regulated[60]. Intriguingly, although E2F1 is best characterized as a transcription factor, E2F1 protein may have a direct role in DNA repair, as suggested by its localization to repair complexes[46, 61]. Thus, it is likely that multiple E2F-regulated mechanisms function in parallel with XRCC1 to stimulate repair. Chen found that enforced E2F expression stimulated XRCC1 levels and that(methylmethane sulfonate) MMS, which induces predominantly heat-labile DNA damage repaired by an XRCC1-mediated BER pathway[62, 63], causes an E2F1-dependent increase in XRCC1 expression. This is consistent with prior reports demonstrating that cellular stress increases endogenous XRCC1 levels [64-66], although this may be cell type-specific [67]. How MMS-induced stress activates the E2F1-XRCC1 axis remains unknown. Cellular sensitivity to MMS may involve an ATR-dependent pathway, and genetic evidence suggests that MMS-induced damage activates the yeast Rad53 (Chk2 human homologue) pathway [68, 69].

Given that the ATM/ATR and Chk2 pathways phosphorylate and activate E2F1 protein[70-73], it is possible that these kinases stimulate XRCC1 expression through E2F1 activation, although this remains to be demonstrated. Interestingly, Chk2-mediated stabilization of the FoxM1 transcription factor stimulates expression of DNA repair genes, including XRCC1 [74]. Given that XRCC1 function is complex, it is likely that its control involves multiple levels. Indeed, posttranslational mechanisms modulate XRCC1 function, as evidenced by the ability of DNA-dependent protein kinase to phosphorylate XRCC1[75] as well as the requirement of protein kinase CK2 to phosphorylate XRCC1 and enhance SSBR and genetic stability [76]. Consistent with the complex control of XRCC1, serum starvation followed by refeeding stimulated XRCC1 expression. This is consistent with cell conditions of high E2F activity but also suggests that serum/mitogenic factors may be important too. This could be a cell typespecific phenomenon, since density arrest and release does not alter XRCC1 levels in human T24 cells[77]. Nevertheless, the biological importance of E2F1 regulation of XRCC1 is suggested by the attenuated *in vivo* DNA repair in E2F1-/-*versus* E2F1+/+MEFs. Two different methods demonstrated reduced DNA repair after MMS-induced DNA damage, which correlates with the decreased XRCC1 levels observed in E2F1-/-cells. The repair of MMS-damaged DNA still occurs in E2F1-/- cells, suggesting that the E2F1-XRCC1 axis is not an absolute requirement in these systems. This is not surprising, given the complex and overlapping repair pathways involved. However, the significance of even a modestly reduced XRCC1-mediated repair function may have important implications for maintaining genomic stability and cell viability. Consistent with this notion of XRCC1 mediating E2F1 activity is the observation that loss of XRCC1 function resulted in an enhanced E2F1-induced apoptotic response in EM9 cells compared with AA8 cells.

Although E2F1 is a damage response protein, it also plays an important role in promoting the expression of a large number of genes required for replication and proliferation [57, 78-80]. Given the intimate relationship between proliferation and replication/repair, the control of XRCC1 by E2F in undamaged cells further integrates SSBR with cell cycle progression as might be expected if enhanced SSBR were necessary to repair SSBs at replication forks [15, 81-83]. Whether and in what context the other E2F family members play a role, as well as what specific SSBR pathways are utilized (*e.g.* long patch BER), remains to be explored.

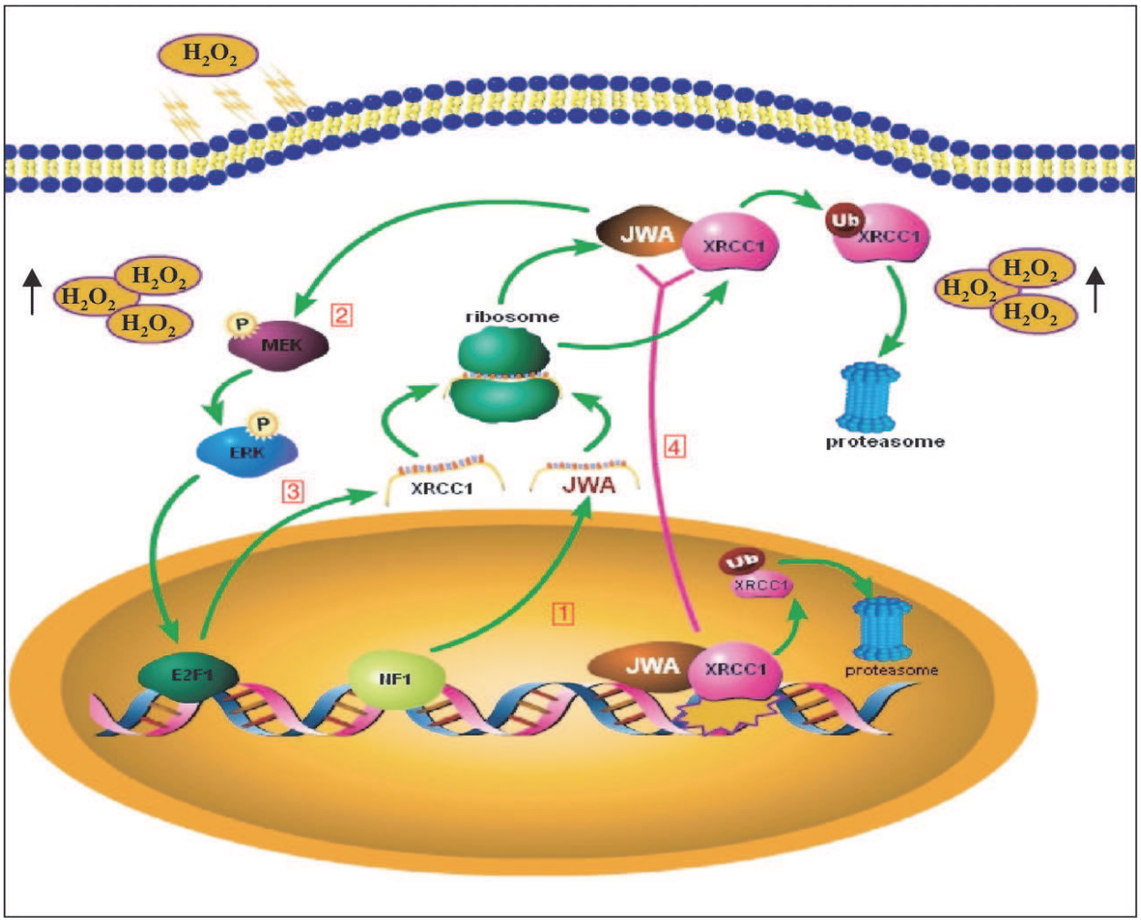


Fig. 4. JWA-E2F1-XRCC1 regulation network in base excision repair

The rapid response of XRCC1-dependent SSBR, especially in S/G2 phase, has been reported [81], and an increased co-localization of XRCC1 with proliferating cell nuclear antigen (PCNA) was observed at sites of replication during S-phase[84]. These results indicate the importance of XRCC1-dependent SSBR and its regulation during the cell cycle. Phosphorylation of E2F1 at serine-31 (S31) in response to DNA damage is required for the activation of ATM-, ATR-and ChK2-dependent DNA damage response pathways [44, 45, 85, 86]. E2F1 has also been suggested to play a potential role in nucleotide excision repair pathway (NER)[54]. Recent reports have shown that XRCC1 is a direct target of E2F1 that is involved in the enhancement of SSBR and BER, which maintain genomic stability and contribute to cell survival[63]. Over-expression of E2F1 has been shown to induce quiescent cells to enter early S-phase and is capable of preventing cells from entering quiescence [87]. Recently, we showed that E2F1 regulates the expression of XRCC1 in response to activation of DNA repair processes, and the exact functional E2F1 binding sites in the XRCC1 promoter region were identified[63]. Certain BER proteins, such as the uracil-DNA glycosylase, have also been demonstrated to be regulated by E2F transcription factors[60]. The fact that enhanced E2F expression stimulates XRCC1-mediated activation of the BER pathway in response to MMS-induced, heat-labile DNA damage suggests it might also be able to promote the expression of a variety of genes involved in DNA replication and cell proliferation.

The p53-E2F network controls and integrates critical functions, such as proliferation, cell cycle checkpoints, apoptosis, and DNA repair [43, 73, 88, 89]. In particular, p53 can promote BER [90, 91], and our discovery that E2F1 may also promote BER expands our understanding of the p53-E2F1 network in regulating DNA repair [63]. Disruption of these cooperative pathways has profound implications for tumorigenesis, as evidenced by enhanced tumor formation in knock-out mouse models for both p53 and E2F1, although intriguingly, both oncogenic and tumor suppressor functions for E2F1 are suggested in compound p53-/- and E2F1-/- mice [73, 92, 93].

The JWA (ARL6IP5)-E2F1-XRCC1 network also plays crucial role in base excision repair [94]. Exposure to oxidative stress increases the generation of intracellular reactive oxygen species, which stimulates NF1 binding to the JWA promoter, enhancing JWA transcription and translation. Then JWA regulates the expression of E2F1, leading to increased transcription of XRCC1. Interactions between JWA and XRCC1 occur in both the cytoplasm and the nucleus when the cells are subjected to oxidative stress (*fig.4*)..

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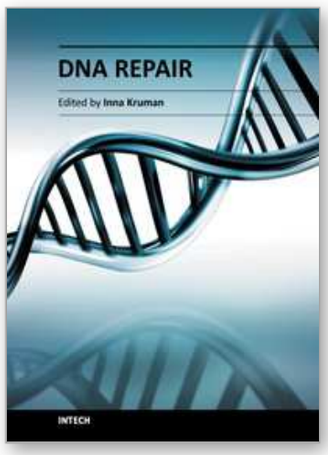
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The book consists of 31 chapters, divided into six parts. Each chapter is written by one or several experts in the corresponding area. The scope of the book varies from the DNA damage response and DNA repair mechanisms to evolutionary aspects of DNA repair, providing a snapshot of current understanding of the DNA repair processes. A collection of articles presented by active and laboratory-based investigators provides a clear understanding of the recent advances in the field of DNA repair.

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