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Review

XPC multifaceted roles beyond DNA damage repair: p53-dependent and p53-independent functions of XPC in cell fate decisions

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ABSTRACT

Xeroderma pigmentosum group C protein (XPC) acts as a DNA damage recognition factor for bulky adducts and as an initiator of global genome nucleotide excision repair (GG-NER). Novel insights have shown that the role of XPC is not limited to NER, but is also implicated in DNA damage response (DDR), as well as in cell fate decisions upon stress. Moreover, XPC has a proteolytic role through its interaction with p53 and casp-2S. XPC is also able to determine cellular outcomes through its interaction with downstream proteins, such as p21, ARF, and p16. XPC interactions with effector proteins may drive cells to various fates such as apoptosis, senescence, or tumorigenesis. In this review, we explore XPC's involvement in different molecular pathways in the cell and suggest that XPC can be considered not only as a genomic caretaker and gatekeeper but also as a tumor suppressor and cellular-fate decision maker. These findings envisage that resistance to cell death, induced by DNA-damaging therapeutics, in highly prevalent *P53*-deficent tumors might be overcome through new therapeutic approaches that aim to activate XPC in these tumors. Moreover, this review encourages care providers to consider XPC status in cancer patients before chemotherapy in order to improve the chances of successful treatment and enhance patients' survival.

1. Introduction

Xeroderma pigmentosum (XP) is a rare autosomal recessive disease caused by a defect in nucleotide excision repair (NER), one of the major DNA repair pathways in the cell. In fact, XP was the first identified human NER-deficient disease and it refers to the parchment-like, dry and freckle-like pigmented skin, i.e. poikiloderma (hyper/hypo pigmentation, atrophy and telangiectasias) [1]. The hallmark of XP disease is an early onset of cutaneous abnormalities at the age of 1.5 years due to a cellular hypersensitivity to UV radiation [2]. Its most prevalent symptoms, which appear at the average age of 8 years, include photosensitivity, cutaneous atrophy and telangiectasia, actinic keratosis and malignant skin neoplasms. A total of 40 % of XP patients showed ocular abnormalities, where 18 % of the reported cases demonstrated neurological anomalies that appeared at a later age [3]. XP complementation groups, XP-A through XP-G, are caused by mutations in genes whose mRNA transcripts encode for the corresponding protein products. In addition, a variant form called XP-V, caused by mutations in the *POLH* gene whose mRNA product encodes polymerase eta (Pol η) protein, which is involved in accurate trans-lesion synthesis of UV-induced DNA damage [4,5].

XP group C or XP-C (OMIM# 278,720) is one of the most common complementation groups accounting for XP disease. XPC was first described in 1933, whereas seven additional complementation groups and their frequencies were reported in 1991 [6]. In the Caucasian population, XP-C accounts for over a third of all XP cases [7]. XP-C is caused by mutations in the *XPC* gene, *i.e.* stop codons, frame shifts, splice-site and missense mutations that result in the total absence of XPC protein, reduction of its levels, or the expression of an inactive XPC protein. The *XPC* gene is located on chromosome 3p25.1 and spans 33 kb, with 16 exons and 15 introns. Mutations in the *XPC* gene are the most common genetic alterations found in European and North African

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XP patients. The XPC protein, made up of 940 amino acids, is an essential DNA damage recognition protein of the NER pathway, in addition to possessing other non-NER functions. Interestingly, Khan et al. revealed an association between an alternatively spliced *XPC* mRNA that skips exon 12 and decreased DNA repair activity in normal cells [8]. This makes XPC not only a key factor used by the cell to defend against DNA damage, but also an important player in many cellular functions including cell fate decisions such as apoptosis, senescence, and tumorigenesis [9–11]. An interesting research study conducted by De Feraudy et al. hypothesized that XPC protein expression is selectively lost in squamous cell carcinomas (SCC) from non-XP-C patients in the general population. Conducting immunohistochemistry on a tissue microarray including SCC, keratoacanthoma and normal skin samples from both immunocompetent and immunosuppressed patients, the authors showed that XPC expression was lost in 49 % of invasive SCC from immunocompetent patients and 59 % of immunosuppressed patients. This loss of XPC expression was correlated with deletions of chromosomal 3p and mutations in the *XPC* gene. The findings of this study suggest that loss or mutation of XPC may be an early event during skin carcinogenesis, providing a selective advantage for initiation and progression of squamous cell carcinomas in non-XP-C patients [12].

Mechanistically, NER repairs a broad spectrum of structurally unrelated bulky DNA lesions and helix-distorting types of damage, making it one of the most essential DNA repair pathways [13–16]. For instance, cyclobutane pyrimidine dimers (CPDs) and pyrimidine-(6,4)-pyrimidone products (6-4PP), caused by UV light, are the most relevant substrates of NER [17,18]. The NER pathway can also repair helix-distorting bulky adducts, such as polycyclic aromatic hydrocarbon (PAH)-DNA adducts, which are generated by exposure to numerous chemicals including alkylating agents [19]. The NER process is complex and encompasses a consortium of over 40 proteins acting in successive steps to eliminate DNA damage. NER is divided into two sub-pathways, global genome NER (GG-NER) and transcription-coupled NER (TC-NER) [20]. GG-NER recognizes and removes DNA lesions throughout the entire genome rendering it a relatively slow process compared to TC-NER. The latter removes lesions in the newly transcribed strand of active genes and is considered to be a fast and efficient process. GG-NER is initiated when XPC, as part of a heterotrimeric protein complex composed of XPC, HR23B and centrin 2, recognizes and binds damaged DNA sites in non-transcribed regions of the genome. In fact, 25–33 % of UV-induced DNA lesions are 6-4PP lesions that are recognized by XPC, while the rest are mainly CPD lesions that are usually recognized by XPC after being recruited by DBB2 [21,22]. In a recent study it was shown that, once tethered to DNA, Rad4 (the XPC ortholog in yeast) can open undamaged DNA without using one or the other of the hairpin motifs in the BHD2 or BHD3 domains. This study also showed that the tethered complex adopts dynamically fluctuating open DNA conformations and the complementary roles of multiple hairpins may offer robustness to the activity of Rad4/XPC when dealing with diverse lesions [23]. In a recent computational study, Panigrahi et al. used molecular dynamics and umbrella sampling simulations to investigate mismatch recognition by Rad4/XPC. The dynamic and energetic characterization of the order and extent of specificity of Rad4/XPC for 3-bp of mismatched sequences demonstrated that Rad4 is highly specific to a mismatch of CCC/CCC, while it recognizes a TTT/TTT mismatch with intermediate specificity and only poorly recognizes TAT/TAT mismatch [24]. Another study showed that XPC binding affinity to DNA bulky lesions is lost when the single nucleotide in the complementary strand opposite the lesion is deleted [25]. Nishimoto et al. recently revealed that deacetylation of histone H3Lys14 (H3K14) by histone deacetylase 3 (HDAC3) after UV-irradiation contributes to XPC recruitment to DNA lesions and promotes GG-NER. Upon UV-irradiation, in HDAC3-depleted cells, XPC accumulation was attenuated and XPC ubiquitylation was inhibited [26]. In another study by Wong et al., it was revealed that, in the repair of UV-induced DNA damage, Vitamin D receptor is required to facilitate dissociation of XPC from damaged DNA, thereby facilitating the normal assembly of the other NER proteins and the completion of GG-NER [27].

For the repair of certain UV-induced DNA lesions (mainly CPDs), the DNA damage binding activity of XPC takes place in the presence of UV-damaged DNA-binding (UV-DBB) protein complex, which contains damage-specific DNA binding 1 (DDB1) and damage-specific DNA binding 2 (DDB2), also known as XPE. In this complex DBB1 does not contact DNA, while DBB2 does [28]. Ribeiro-Silva et al. showed that XPC recognition of DNA damage not only depends on lesion binding by DDB2, but also on timely DDB2 dissociation by ubiquitylation. In addition, TFIIH complex further promotes DDB2 dissociation allowing the handover of damaged DNA to XPC and the formation of an XPC-TFIIH damage verification complex [29]. Another study indicated that the ubiquitin-proteasome system (UPS) is important for the DDB2-mediated lesion recognition sub-pathway but is not required for the GG-NER pathway initiated through direct lesion recognition by XPC [30]. Consistent with this, a recent study demonstrated that the tumor suppressor protein USP44 is required for CPD repair, but not 6-4PP repair. USP44 directly deubiquitinates DDB2, thereby facilitating DBB2 binding to CPD lesions and the subsequent recruitment of XPC [31]. Nevertheless, UV-DDB is suppressed in numerous rodent cells due to mutation in the *p48* gene. Transfection of *p48* into hamster cells conferred onto them UV-DDB activity and enhanced the removal of CPDs from genomic DNA and from the non-transcribed strand of an expressed gene. Expression of p48 suppressed UV-induced mutations arising from the non-transcribed strand; however, it had no effect on cellular UV sensitivity. Similarly, p48 was shown not to be required for TC-NER of CPDs [32]."

Following the DNA damage recognition step in GG-NER, XPC recruits the TFIIH protein complex, which contains XPB and XPD DNA helicases, thereby unwinding the DNA helix and facilitating the entrance of the pre-incision complex to the lesion site [33]. However, some studies have demonstrated that XPD is not part of the TFIIH complex. XPD is usually part of a separate protein complex that also contains the cdk-activating kinase (CAK). This latter complex is composed of CDK7/cyclinH/MAT1, and is responsible for phosphorylating the C-terminal domain of RNA polymerase II during transcription [34]. Recently, nuclear magnetic resonance spectroscopy was used to examine the interactions of pleckstrin homology (PH) domain of p62 (the core subunit of human TFIIH), providing structural and dynamic insights into the TFIIH mechanism of action. It was found that TFIIH interacting partners use the pH domain of p62 to recruit TFIIH [35]. Next, the verification of a DNA lesion is mediated by subsequent binding of XPA [36]. The latter presents docking sites for the endonucleases XPG and excision repair cross-complementation group 1 (XPF-ERCC1). In addition, XPA binds to replication protein A (RPA), a single-strand DNA binding protein complex that facilitates the correct positioning of repair proteins [37,38]. In the following step, dual DNA incisions are made by XPG and ERCC1-XPF, at the 3′- and 5′-ends of the lesion, respectively [39], resulting in the excision of a 24–32 single stranded DNA fragment containing the damaged site [40]. Thereafter, the gap is filled by DNA polymerases (Pol δ, Pol ε, and Pol κ), whose functions are facilitated by proliferating cell nuclear antigen (PCNA), RPA, and replication factor C (RFC) [41]. The final step involves DNA ligation by DNA ligase, which closes the 3′ nick leading to restoration of the original DNA fragment [42]. Overall, XPC is the initiator of GG-NER through its DNA damage recognition capacity.

2. XPC in DDR

The DDR represents an evolutionary conserved group of signaling pathways that are turned on immediately after sensing a DNA lesion. DDR is continuously active to ensure genomic stability of cells and includes activation of cell cycle checkpoints, apoptosis, and senescence [43]. Multiple lines of evidence show that XPC can influence cell-fate decisions through interaction with the molecular effectors of the DDR response.

2.1. P53 role in NER

P53 is a tumor suppressor that integrates many stress signals, allowing it to be a genome gate-keeper and a decision-maker of cell life or death [44]. It is activated by many stress pathways including DDR. In fact, p53 is a central regulator of DDR and one of its most crucial players [45]. Under normal physiological conditions, p53 is short lived and can be ubiquitinated by proteins such as the murine double minute 2 (MDM2) before being targeted for degradation through ubiquitin-dependent proteolysis by the 26S proteasome [46]. P53 is an integrator of many upstream stress pathways that usually modify it at the transcriptional and translational levels and can cause its post-translational modification (PTM). For example, p53 is stabilized by several PTMs during DDR [45].

P53 responds to numerous kinds of DDR signaling, including UV-induced DNA damage. DDR signaling can lead to phosphorylation of p53, hindering its interaction with MDM2; p53 is no longer ubiquitinated, becomes stable, accumulates in the nucleus, and is activated to trigger its downstream effects [47,48]. During DDR signaling, phosphorylation of p53 serine 15, by ataxia-telangiectasia mutated (ATM) or ATM and Rad3-related (ATR) kinases, or serine 20, by the checkpoint kinase (CHK2), inhibits p53 interaction with MDM2 [48]. Upon DNA damage, p53 triggers an array of events, such as transcription induction, cell cycle arrest, DNA repair, senescence, or apoptosis, that lead to the restoration of genomic integrity [27,28].

Outcomes of p53 activation are intricate and differ depending on the type of cells undergoing DNA damage, the cell cycle stage, the extent of DNA damage, the speed of its repair, and the strength and duration of p53 activation [49]. P53 was shown to be activated not only by IR-induced DNA damage, but also by other classes of DNA damage, including UV-induced DNA damage. This was the first indication that p53 may be involved in NER pathway [50]. However, a direct link between p53 activation and NER was not evident until Smith et al. found that p53-deficient cells were sensitive towards UV-induced DNA damage and could not repair the induced DNA damage [51]. Thereafter, Ford et al. investigated the effects of *TP53* mutations on cellular sensitivity to UV-irradiation and on NER in primary human skin fibroblasts from patients with Li-Fraumeni syndrome (LFS). LFS patients inherit a germline mutation in one allele of the *TP53* gene and exhibit an increased risk for developing a variety of neoplasias at an early age in addition to the loss of the second copy of wild-type *TP53* gene. Ford et al. used two sets of cultured LFS cell lines, expressing only mutant *TP53*. The LFS cells showed resistance to UV-induced cytotoxicity, apoptosis and deficiency in global NER, as was manifested by the reduced removal of CPDs, as compared to *TP53* heterozygous counterparts [52]. Subsequent studies revealed that p53 was required for the regulation of GG-NER, but largely dispensable for TC-NER [53–56]. Later, several groups described the importance of the p53-mediated NER mechanism for protection against mutagenesis [50].

By now, it is known that p53 is important in UV-induced DNA damage repair and GG-NER through a transcriptional regulation mechanism including both trans-activation and trans-repression activities. Also, p53 can be involved in NER through actions not directly related to gene regulation and this suggests transcription-independent roles for p53 in DNA repair [45]. In fact, p53 can upregulate *DDB2* and *XPC* mRNA levels supporting its involvement in GG-NER via its trans-activation activity [57–60]. The transcription-independent functions of p53 in NER could be direct or indirect, through p53 activation of its downstream effectors such as MDM2 or GADD45. Studies have ascribed p53 transcription-independent involvement in GG-NER to its effects on the helicase activities of XPB and XPD [61,62], as well as its role on chromatin accessibility [63]. Other studies showed that p53 can directly interact with TFIIH components such as XPD and XPB, as well as CSB [61]. Also, p53 has been shown to interact with RPA [64]. Above all, p53 activity has been shown to be required for the recruitment of XPC and TFIIH to DNA damage sites. In addition, it was suggested that p53 exerts this role, at least partly, through transcriptional activation of its downstream effector DBB2 [65]. It is clear now that p53 has robust interactions with GG-NER machinery, consequently this review focuses on the interactions between XPC and p53, and discusses their possible reciprocal crosstalk.

2.2. XPC-p53 interaction: a feedback loop

2.2.1. Transcriptional regulation of XPC by p53

Ford et al. found that p53 is important to the functionality of GG-NER, but not TC-NER [53]. Their results showed that UV-irradiated human fibroblasts homozygous for *TP53* mutations were not able to repair CPDs or 6-4PPs. However, fibroblasts heterozygous for *TP53* mutations were able to repair 6-4 PPs and showed decreased rates of repair of CPDs compared to normal cells. Furthermore, the study showed that withdrawal of tetracycline from a homozygous mutant cell line containing tetracycline-regulated wild type (WT) p53 gene lead to induction of p53 expression, which allowed the repair of CPDs and 6-4PPs but did not alter TC-NER of CPDs [53]. Later, Adimoolam and Ford demonstrated that an intimate relationship exists between XPC and p53. Indeed, p53 competent UV-irradiated human fibroblasts and colorectal cancer cells showed an increase in *XPC* expression at the RNA and protein levels compared to p53-deficient cells [58]. Interestingly, re-expression of WT p53 in $p53^{null}$ human fibroblasts derived from an LFS individual significantly increased the expression of XPC protein [58]. Moreover, the same study revealed the existence of a putative p53 response element in the *XPC* promoter that was capable of mediating sequence-specific *TP53* DNA binding *in vitro*. Furthermore, Fitch et al. showed that p53, already known to regulate the transcriptional expression of *XPC* and *DDB2*, does not itself directly interact with the UV-induced damaged DNA site [60]. Remarkably, the result of the study showed that p53 downstream effectors, XPC and p48, encoded by DDB2, are the proteins that bind to the DNA lesions caused by UV-irradiation [60], noting that p48 itself enhanced XPC binding to the DNA lesions [60].

Other studies showed a link between XPC and p53 using DNA damaging agents other than UV. For instance, Forrester et al. investigated the transcriptional response of DNA repair upon exposure to ionizing radiation (IR) and found that p53 played a major role in the induction of *XPC* transcription levels and in the formation of a shorter alternative XPC transcript [66]. The protein product of this shorter transcript (NCBI protein id: CAA46158.1) is predicted to be missing the first 117 amino acids from the N-terminus of the full length XPC protein isoform. It is worth noting that the N-terminus region of the normal XPC protein contains several coiled-coil regions whose function has not been well characterized. In the full length XPC, it is known that amino acid residues 156–325 interact with DNA and XPA, while its C-terminus (residues 492–940) binds to DNA and also interacts with various XPC protein partners including RAD23B, CENTN2, and TFIIH. In addition, Amundson et al. showed that WT p53 is indispensable for the induction of *XPC* expression in human peripheral blood lymphocytes exposed to gamma-rays [67]. Moreover, Batista et al. revealed an up-regulation of *XPC* and *DDB2* mRNAs in *TP53* WT, but not *TP53* mutant glioma cells, in response to the chloroethylating nitrosourea agent, nimustine. This finding indicated that p53 regulates a pathway that involves these DNA repair proteins [68]. Another study by Batista et al. shows that UV-C irradiation of *TP53* WT glioma cells caused a 9-fold increase in XPC protein levels, in comparison to *TP53* mutant cells, in which XPC was increased only 1.1-fold [69]. The *TP53* mutant cells showed increased apoptosis upon UV-exposure due to decreased NER efficiency and reduced levels of photoproduct repair [69]. The apoptosis is executed by Bcl-2 degradation and sustained Bax and Bak up-regulation [69].

A newer study by Barckhausen et al. has showed that p53-dependent upregulation of XPC- and DDB2-mediated DNA repair allows malignant melanoma cells to acquire resistance to DNA-crosslinking chemotherapeutic agents [70]. In particular, XPC and DDB2 induction by p53 was

observed after melanoma therapy using the cross-linking anticancer drugs fotemustine, cisplatin and mafosmide, and resulted in sustained survival of the cells and chemoresistance [70]. However, cells mutated for *TP53* were unable to repair interstrand crosslinks (ICLs) leading to prolonged ATM, ATR and CHK1 activation, and finally apoptosis [70]. On the other hand, the same study showed that the increase of DDB2 and XPC levels does not confer chemoresistance to methylating anticancer drugs, such as dacarbazine (DTIC) and temozolomide [70].

UV-DDB requires the expression of two subunits, p127 (or DDB1) and p48 (or DDB2). In normal cells, p48 expression is rate limiting for UV-DDB and its transcription is induced by the p53-dependent response to DNA damage [57]. It is noteworthy that specific biochemical differences exist between rodent and human DNA repair. A study on rodents, using hamster cells, by Tang et al. previously demonstrated that a mutant *p48* (or *DDB2*) gene leads to very low levels of UV-DDB and that GGR of CPDs is deficient. Therefore, the validity of rodent models for assessing cancer risk in humans has been questioned [32]. Another study inspected the *in vivo* binding properties of p48 and XPC. p48 was shown to bind both 6-4PP and CPD lesions with a slight preference for 6–4PP, whereas XPC revealed a very strong binding preference for 6–4PP over CPD. Interestingly, the binding properties of XPC were dramatically altered following the overexpression of p48 or through upregulation of p53 after DNA damage, resulting in significant colocalization of XPC within CPD-only-containing sites [21].

2.2.2. *XPC expression level can affect p53 expression or stability*

As mentioned above, several studies revealed that XPC can regulate p53 levels or activity. For instance, Wu et al. showed that the presence of a defective XPC could lead to p53 dysfunction, which in turn enhanced lung adenocarcinoma metastasis [71]. In this study, XPC modulated p53 transcriptional activity by stabilizing the formation of the HR23B-p53 complex, which prevented p53 degradation. Moreover, XPC overexpression repressed p53-induced matrix metalloproteinase-1 (MMP1) transcription, leading to the suppression of the metastatic ability of xenografted lung cancer cells in nude mice [71]. Another study by Krzeszinski et al. uncovered a critical role of XPC in regulation of p53 turnover. The mechanism by which XPC regulates p53 turnover is through its direct interaction with MDM2, which in turn ubiquitinates p53. Ubiquitinylated p53 is then recruited to the stable Rad23-XPC complex, which in turn delivers it to the proteasome for degradation [65]. The same study shows that p53 becomes stabilized in normal cells upon UV irradiation, however, in cells expressing higher levels of XPC, p53 is degraded [72]. This result underscores a critical function of XPC in proteolysis and an existence of an interplay between protein degradation and DNA repair [72]. Thus regulation of XPC transcription by p53, and regulation of p53 turnover by XPC indicates an existence of a negative feedback loop between XPC and p53 (Fig. 1). Notably, Nahari et al. discovered the presence of a mutational hotspot at a non-dipyrimidinic CpG site in codon 122 of the *Trp53* gene in UVB-induced skin tumors from *Xpc*$^{-/-}$ mice, but not from *Xpa* or *Csa* mutant mice. Since this mutational hot spot in the *p53* gene is not at a dipyrimidine site and is apparently Xpc-specific, Nahari et al. suggested that XPC is involved in repair of non-dipyrimidine base damage, apart from its known function in NER [73].

Microarray analysis of normal human fibroblasts and two XPC-defective fibroblast cell lines revealed that, upon cisplatin treatment, the XPC defect affected primarily cell cycle and cell proliferation-related genes to greater extent than genes of other cellular functions. Importantly, the XPC defect reduced p53-mediated responses to cisplatin treatment and attenuated phosphorylated p53 levels, caspase-3 activation, and p21 responses [74]. Interestingly, p53 phosphorylation has been shown to be involved in the XPC protein DNA damage recognition-mediated signal transduction process [74]. These results suggest that DNA damage recognition by XPC protein followed by formation of the XPC-TFIIH complex result in an enhanced interaction of TFIIH with p53 [62]. TFIIH triggers the phosphorylation of p53 protein by CDK7 [75,76], leading to the subsequent activation of the p53 signal transduction pathway.

2.3. *Role of XPC in cellular outcome*

Several studies have shown the importance of interaction between XPC and tumor suppressor genes, reflecting the role of XPC in cellular maintenance, prevention of tumor growth, and determination of cellular outcome. A study by Rezvani et al. demonstrated that XPC-silencing in normal human keratinocytes leads to metabolism remodeling, increased oxidative stress, and an increase in the expression of cell cycle inhibitors p16, p21 and p-cdc2, thereby causing a peak of apoptosis [77]. Moreover, a recent study in mice showed that after chronic cigarette smoking exposure, the expression of XPC was decreased, promoting the

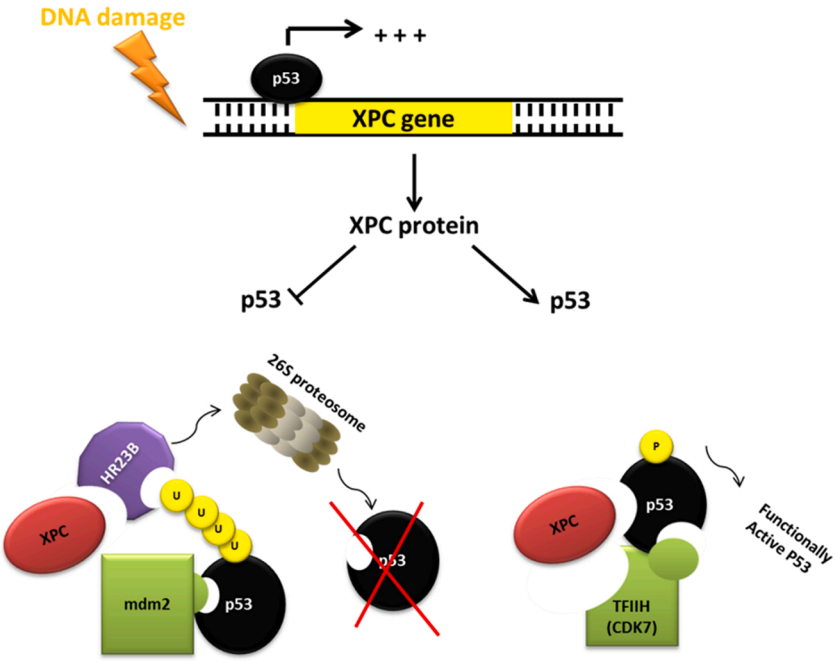

Fig. 1. XPC interaction with p53. Transcription of the *XPC* gene constitutively, or upon UV exposure, is regulated by p53. XPC protein activates p53 by mediating its interaction with the CDK7 kinase subunit of TFIIH complex, which will phosphorylate p53 (right panel). On the other hand, XPC protein downregulates p53 protein by localizing it in close proximity to MDM2 protein, which will ubiquitinylate it, thereby allowing its recognition by HR23B that will target ubiquitinated p53 towards degradation by the 26S proteasome (left panel).

development of emphysema, a disease characterized by the loss of lung parenchyma cells [78].

XPC expression has also been implicated in chemoresistance. A recent study on human lymphoblastoid TK6 cells showed that *XPC*$^{-/-}$ cells were highly sensitive to different genotoxic agents, such as UV-C light and 2-amino-1-methyl-6-phenylimidazo [4,5-b] pyridine (PhIP), highlighting the importance of XPC expression in protection of cells against genotoxicity [79]. In addition, treatment of gastric cell lines MKN-45 and AGS with cisplatin showed that the more sensitive cell line (MKN-45) possessed an impaired NER pathway due to low-level expression levels of XPC. This suggests that NER might be a potential target to improve the response of gastric cancer cells to cisplatin treatment [80]. Moreover, XPC was involved in the reversal of the cisplatin (DDP) resistance in drugresistant A549/DDP lung adenocarcinoma cells. High XPC expression was noted in A549/DDP cells compared to parental A549 cells and was associated with DDP resistance. XPC knockdown using siRNA in A549/DDP cells inhibited their proliferation, increased induction of apoptosis and decreased the expression levels of the PI3K/Akt/mTOR signaling proteins. The results of the study show clearly that XPC inhibition can cure DDP resistance in A549/DDP cells and improve efficacy of chemotherapy [81].

The effect of XPC on the cellular outcome could be managed through either p53-dependent or -independent mechanisms.

2.3.1. *P53-dependent effects of XPC on cellular outcome*

The prominent interaction of XPC with the tumor suppressor p53 affects indirectly the whole cellular outcome through downstream p53 signaling (Fig. 2). Upon activation of p53, cells can undergo transient cell-cycle arrest as a result of induction of the cyclin-dependent kinase inhibitor p21. In addition, cells can undergo apoptosis as a result of induction of the pro-apoptotic BCL2 gene family members, such as BAX, PUMA and NOXA. Moreover, cells can undergo senescence through stimulation of the cyclin-dependent kinase inhibitor p16^{Ink4a} and the tumor suppressor gene p19^{ARF} [82,83]. Furthermore, mice mutated for both *XPC* and *Trp53* and exposed to UV-irradiation showed accelerated skin cancer development compared to *XPC* mutant mice with WT *p53* expression [84].

A research study conducted by Nollen et al. showed that exposure of human skin fibroblasts to the carcinogen arsenite, and its more prevalent metabolite, monomethyllarsonous acid (MMAIII), led to a decrease in XPC transcript and protein levels, as well as XPC localization to sites of UV-C DNA damage. However, the same carcinogenic exposure led to increased p53 expression [85]. The results of this study suggest not only a link between XPC and p53 under arsenic exposure but also a role of XPC in cancer prevention.

Several studies have demonstrated an interaction between *XPC* deficiency and the loss of *P53* during cancer development. Using an improved PCR-single strand conformation polymorphism analysis, Giglia et al. detected mutations of *TP53* in 58 skin biopsies and three primary internal tumors from XP-C patients [86]. This study also showed that *TP53* mutations occur at a significantly higher frequency in skin tumors of XP-C patients (85 %) compared with skin tumors from XP patients not in group C (33 %). A more recent study by Sarasin et al. showed that XP-C patients with myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) had a familial predisposition to somatic *TP53* mutations [87]. The study found that out of 161 XP-C patients 13 of them (~8 %) developed MDS, AML, or T-cell acute lymphoblastic leukemia (T-ALL) at ages ranging from 7 to 29 years. Importantly, out of these 13 MDS or AML patients, a total of 5 patients had deleterious somatic *TP53* mutations [87]. Recently, Yurchenko et al. conducted whole-genome sequencing of a collection of internal XP-C tumors consisting of 6 leukemias and 2 sarcomas [88]. This study showed that 7 out of 8 samples harbored a founder c.1643_1644 delTG mutation, characteristic of this XP-C population, and that the patients developed internal tumors early in life, between 12 and 30 years of age. Further analysis showed that XP-C cancers contained somatic copy number aberrations (SCNAs) and *TP53* mutations characteristic of sporadic malignancy. A comparison of XP-C leukemias and a cohort 15 adults with de novo AML leukemias (WT *XPC*) found that the frequency of *TP53* mutations was significantly higher in XP-C leukemias [88].

2.3.2. *P53-independent effects of XPC on cellular outcome*

XPC role in cellular fate decision can also be established through mechanisms independent of p53. Several studies have investigated the interaction between XPC and effector proteins other than p53, in mechanisms that governs the cellular outcome under conditions of

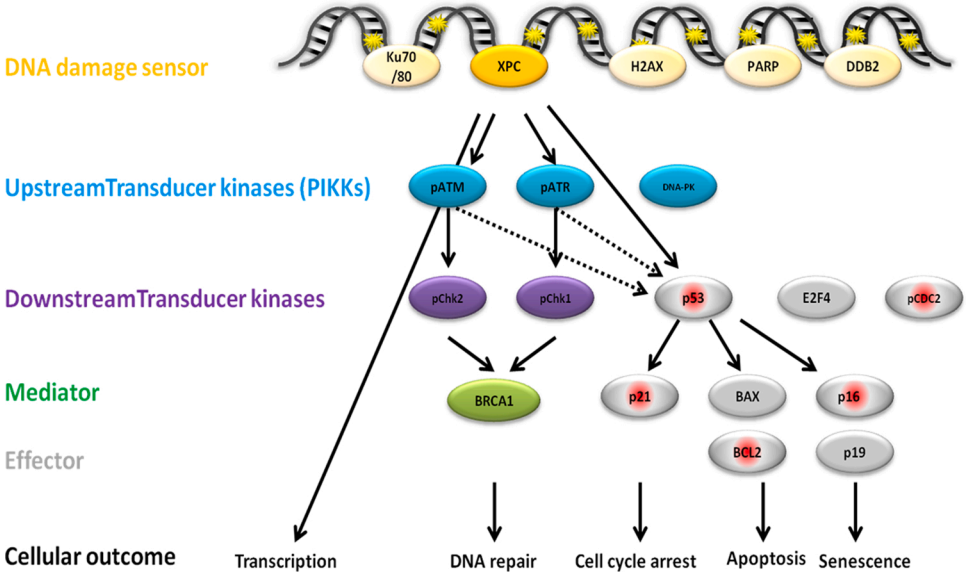

Fig. 2. XPC determines cell fate through its impact on the DDR response. XPC interacts with other DNA damage sensor proteins such as Ku70/80, H2AX, PARP and DDB2. Downstream of DDR, XPC interacts with transducers, such as ATM and ATR kinases, inducing their activation by phosphorylation. There is also evidence suggesting an interaction between XPC and DNA-PK. Activated ATM and ATR will subsequently activate their substrates Chk2 and Chk1, respectively, which will activate mediator protein BRCA1. Upon its activation, BRCA1 will provoke DNA repair. On the other hand, XPC also interacts with p53, either activating it or mediating its degradation. XPC interacts with effector E2F4 which inhibits XPC transcription. XPC downregulates the expression of inhibitors of cell-cycle progression genes, such as *CDC2*, the human homolog of cyclin-dependent kinase 1 (*Cdk1*), leading to inhibition of cell cycle progression. Downstream, XPC interacts with p21, directly or indirectly through p53, thereby mediating cell-cycle arrest. Similarly, XPC interaction with p16 and p19 provokes cell senescence. XPC also mediates apoptosis through its interaction with anti-apoptotic BCL2 and apoptotic BAX proteins. In addition, XPC affects cellular outcome by influencing cellular transcription processes. Therefore, a defect in XPC could perturb cellular integrity and target cells toward either death or carcinogenesis. Note: Red labeling of some items demonstrates the presence of feedback interaction with XPC.

stress. For instance, Wang et al. demonstrated that XPC has a novel function as a potent enhancer of apoptosis in absence of any influence by p53. Mechanistically, XPC downregulates anti-apoptotic casp-2S, the short isoform of caspase-2, at both the RNA and protein levels through inhibition of its promoter activity. This enhanced the DNA-damage induced activation of casp-9 and casp-6 which ultimately leads to cell death. In addition, the same study inspected the effect of overexpressing XPC in various human cancer cell lines of different p53 status and analyzed cisplatin-induced apoptosis. XPC overexpression enhanced the cisplatin-induced apoptosis in p53-deficient human ovarian carcinoma cells SKOV3 and human non-small cell lung carcinoma cells H1299, as well as p53 heterozygous ovarian carcinoma cells A2780/CP70. However, XPC overexpression did not exhibit augmented apoptosis in p53-proficient A549 cells upon cisplatin treatment. These data indicated that elevation of XPC level in p53-deficient cancer cells can overcome their resistance to cisplatin [89]. Moreover, XPC has also been shown to be a target for the tumor suppressor known as alternative reading frame (ARF), which is derived from an alternative reading frame of the INK4A locus that encodes two tumor-suppressor proteins, $p16^{INK4a}$ and $p19^{ARF}$. It has been proven that ARF mediates its gatekeeper tumor suppressor activity occurs by inhibiting MDM2, a negative regulator of p53, leading to the activation of the p53 transcriptional program, and resulting in cell-cycle arrest or apoptosis. Interestingly, ARF possesses an important function in NER, independent of p53, through increased expression of XPC. Mechanistically, ARF reduces the interaction between the E2F4-p130 repressor complex and the XPC promoter, triggering XPC expression [90,91]. Thus, the XPC pathway is one of the pathways that enable ARF-mediated tumor suppressor function. Furthermore, a prominent study by Ming et al. showed that the tumor suppressor *SIRTUIN 1* (SIRT1), which is an NAD-dependent longevity promoting deacetylase, regulates GG-NER through XPC. Specifically, SIRT-1 reduces AKT-dependent nuclear localization of the E2F4-p130 complex, which is a transcription repressor of XPC, thereby enhancing XPC expression [92].

Furthermore, an interesting research study by Stout et al. showed that XPC is implicated in cellular outcome through its involvement in telomere stability [93]. Upon exposure to chronic UV-irradiation, the skin of $Xpc^{-/-}$ mice had shorter telomeres compared with wild-type skin. Surprisingly this effect was reversed by additional deficiency in telomerase in which $Xpc^{-/-}$G1-G3Terc$^{-/-}$(Xpc and telomerase double knock out) mice [93] had aberrantly long telomeres due to activation of the alternative lengthening of telomeres (ALT pathway) which can lead to increased tumor incidence. As evidence of this, the double deficiency mice displayed an elevated incidence of UV-induced mutant p53 patches, known precursor lesions for skin tumors. It was also found that in the absence of UV-irradiation, Xpc is required to prevent telomeric aberrations and recombination at telomeres, suggesting a role for Xpc in telomere stability [93].

Several studies have investigated the roles of XPC in oxidative stress, mutagenesis and response to cancer therapy. Fayyad et al. investigated the role of XPC in oxidative stress by studying the effect of different XPC mutations on base excision repair (BER), the pathway primarily responsible for repair of oxidative DNA damage [94]. Immediately post-UVB-irradiation, primary fibroblasts derived from XP-C patients exhibited a downregulation in mRNA and protein levels of different BER factors (OGG1, MYH, and APE1), along with increased 8-oxoguanine levels. Another study by Yurchenko et al. analyzed a collection of internal XP-C tumor genomes (6 leukemias and 2 sarcomas), using whole-genome sequencing (WGS) [88]. This study showed that XPC deficiency increased the risk of hematologic malignancies, where a specific mutational pattern and an average 25-fold increase in mutation rates was observed in XP-C versus sporadic leukemias [88]. By conducting germline and tumour whole-exome sequencing (WES) on 44 stage III/IV melanoma patients, Aoude et al. demonstrated that XPC is one of the pathogenic germline variants associated with poor overall survival [95]. Furthermore, investigation of the role of XPC in anti-angiogenesis treatment of human non-small-cell lung cancer (NSCLC) [96] revealed that down-regulation of XPC by 17-allylamino-17-demethoxygeldanamycin (17-AAG) enhanced the cytotoxic action of bevacizumab, a VEGF antibody that inhibits angiogenesis. It was concluded that downregulation of XPC levels increased tumor response to anti-angiogenesis therapy and prolonged the overall survival of NSCLC patients. In similar context, Yunyao et al. showed that treatment of NSCLC by oroxylin A inhibits hypoxia-inducible factor 1 alpha (HIF-1α)-mediated transcription of XPC, thus downregulating XPC levels and overcoming hypoxia-induced cisplatin resistance [97]. This study supports an important role for XPC-dependent NER in hypoxia-induced cisplatin resistance and provides a novel treatment strategy for cisplatin resistant NSCLC tumors.

3. Conclusions

XPC is traditionally recognized for its DNA damage recognition capacity as the initiator of GG-NER. In this review, we show that XPC can influence cell-fate decisions through interaction with the molecular effectors of the DDR response, especially p53. Multiple research studies show that XPC interacts with p53 in a feedback loop, involving transcriptional regulation of XPC by p53 as well as XPC expression level impacting p53 expression and/or stability. In addition, XPC interacts with several downstream molecules of p53 and with other tumor suppressors. Our review sheds light on XPC involvement in mutagenesis and chemoresistance as well as telomere stability and oxidative stress. Therefore, XPC can be considered not only a genomic caretaker but also a cell-fate decision maker. Finally, the findings of this review paper and the critical analysis of the large number of research studies on XPC enable us to strongly suggest that XPC status should be considered in cancer patients before chemotherapy in order to improve the chances of successful treatment and enhance patients' survival.

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors gave their consent for the publication of this review article.

Availability of data and material

Not applicable.

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Authors' contributions

All authors participated in the writing of the review article. KZ designed the plan and the content of the article. AZ wrote the first draft with help of MED and AS. FM and HRR corrected the first draft. KZ supervised the work and corrected the final version.

Declaration of Competing Interest

The authors declare that they have no competing financial or non-financial interests.

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References

[1] J.E. Cleaver, Defective repair replication of DNA in xeroderma pigmentosum, Nature 218 (1968) 652–656, https://doi.org/10.1038/218652a0.

[2] J.S.C. English, A.J. Swerdlow, The risk of malignant melanoma, internal malignancy and mortality in xeroderma pigmentosum patients, Br. J. Dermatol. 117 (1987) 457–461, https://doi.org/10.1111/j.1365-2133.1987.tb04925.x.

[3] K.H. Kraemer, Xeroderma pigmentosum. Cutaneous, ocular, and neurologic abnormalities in 830 published cases, Arch. Dermatol. 123 (1987) 241–250, https://doi.org/10.1001/archderm.123.2.241.

[4] E.A. De Weerd-Kastelein, W. Keijzer, D. Bootsma, Genetic heterogeneity of xeroderma pigmentosum demonstrated by somatic cell hybridization, Nat. New Biol. 238 (1972) 80–83, https://doi.org/10.1038/newbio238080a0.

[5] J.E. Cleaver, Cancer in xeroderma pigmentosum and related disorders of DNA repair, Nat. Rev. Cancer 5 (2005) 564–573, https://doi.org/10.1038/nrc1652.

[6] E.A. Cockayne, Inherited abnormalities of the skin and its appendages, Am. J. Surg. 21 (1933) 142, https://doi.org/10.1016/s0002-9610(33)90590-5.

[7] L. Li, E.S. Bales, C.A. Peterson, R.J. Legerski, Characterization of molecular defects in xeroderma pigmentosum group C, Nat. Genet. 5 (1993) 413–417, https://doi.org/10.1038/ng1293-413.

[8] S.G. Khan, V. Muniz-Medina, T. Shahlavi, C.C. Baker, H. Inui, T. Ueda, S. Emmert, T.D. Schneider, K.H. Kraemer, The human XPC DNA repair gene: arrangement, splice site information content and influence of a single nucleotide polymorphism in a splice acceptor site on alternative splicing and function, Nucleic Acids Res. 30 (2002) 3624, https://doi.org/10.1093/NAR/GKF469.

[9] A. Zebian, A. Shaito, F. Mazurier, H.R. Rezvani, K. Zibara, XPC beyond nucleotide excision repair and skin cancers, Mutat. Res. - Rev. Mutat. Res. 782 (2019), https://doi.org/10.1016/j.mrrev.2019.108286.

[10] C. Masutani, K. Sugasawa, J. Yanagisawa, T. Sonoyama, M. Ui, T. Enomoto, K. Takio, K. Tanaka, P.J. van der Spek, D. Bootsma, Purification and cloning of a nucleotide excision repair complex involving the xeroderma pigmentosum group C protein and a human homologue of yeast RAD23, EMBO J. 13 (1994) 1831–1843, https://doi.org/10.1002/j.1460-2075.1994.tb06452.x.

[11] M.K.K. Shivji, J.G. Moggs, I. Kuraoka, R.D. Wood, Assaying for the dual incisions of nucleotide excision repair using DNA with a lesion at a specific site, Methods Mol. Biol. 314 (2006) 435–456, https://doi.org/10.1385/1-59259-973-7:435.

[12] S. De Feraudy, K. Ridd, L.M. Richards, P.Y. Kwok, I. Revet, D. Oh, L. Feeney, J. E. Cleaver, The DNA damage-binding protein XPC is a frequent target for inactivation in squamous cell carcinomas, Am. J. Pathol. 177 (2) (2010) 555–562, https://doi.org/10.2353/ajpath.2010.090925. Aug.

[13] K. Sugasawa, Mechanism and regulation of DNA damage recognition in mammalian nucleotide excision repair. Enzymes, Academic Press, 2019, pp. 99–138, https://doi.org/10.1016/bs.enz.2019.06.004.

[14] P.C. Hanawalt, Subpathways of nucleotide excision repair and their regulation, Oncogene 21 (2002) 8949–8956, https://doi.org/10.1038/sj.onc.1206096.

[15] M. Kusakabe, M.F, Yuki Onishi, Haruto Tada, Fumika Kurihara, Kanako Kusao, S. Iwai, W.S, K.S, Masayuki Yokoi, Mechanism and regulation of DNA damage recognition in nucleotide excision repair, Genes Environ. 41 (2019).

[16] J. De Boer, J.H.J. Hoeijmakers, Nucleotide Excision Repair and Human Syndromes, 2000.

[17] H.L. Lo, S. Nakajima, L. Ma, B. Walter, A. Yasui, D. Ethell, L.B. Owen, Differential biologic effects of CPD and 6-4PP UV-induced DNA damage on the induction of apoptosis and cell-cycle arrest, BMC Cancer 5 (2005), https://doi.org/10.1186/1471-2407-5-135.

[18] D. Chandrasekhar, B. Van Houten, In vivo formation and repair of cyclobutane pyrimidine dimers and 6-4 photoproducts measured at the gene and nucleotide level in Escherichia coli, Mutat. Res. - Fundam. Mol. Mech. Mutagen. 450 (2000) 19–40, https://doi.org/10.1016/S0027-5107(00)00014-2.

[19] G. Spivak, Nucleotide excision repair in humans, DNA Repair (Amst). 36 (2015) 13–18, https://doi.org/10.1016/j.dnarep.2015.09.003.

[20] T. Iyama, D.M. Wilson, DNA repair mechanisms in dividing and non-dividing cells, DNA Repair (Amst). 12 (2013) 620–636, https://doi.org/10.1016/j.dnarep.2013.04.015.

[21] M.E. Fitch, S. Nakajima, A. Yasui, J.M. Ford, In vivo recruitment of XPC to UV-induced cyclobutane pyrimidine dimers by the DDB2 gene product, J. Biol. Chem. 278 (2003) 46906–46910, https://doi.org/10.1074/jbc.M307254200.

[22] M. Wakasugi, A. Kawashima, H. Morioka, S. Linn, A. Sancar, T. Mori, O. Nikaido, T. Matsunaga, DDB accumulates at DNA damage sites immediately after UV irradiation and directly stimulates nucleotide excision repair, J. Biol. Chem. 277 (2002) 1637–1640, https://doi.org/10.1074/jbc.C100610200.

[23] D. Paul, H. Mu, A. Tavakoli, Q. Dai, X. Chen, S. Chakraborty, C. He, A. Ansari, S. Broyde, J.H. Min, Tethering-facilitated DNA "opening" and complementary roles of β-hairpin motifs in the Rad4/XPC DNA damage sensor protein, Nucleic Acids Res. 48 (2021) 12348–12364, https://doi.org/10.1093/nar/gkaa909.

[24] A. Panigrahi, H. Vemuri, M. Aggarwal, K. Pitta, M. Krishnan, Sequence specificity, energetics and mechanism of mismatch recognition by DNA damage sensing protein Rad4/XPC, Nucleic Acids Res. 48 (2020) 2246–2257, https://doi.org/10.1093/nar/gkaa078.

[25] K.M. Feher, A. Kolbanovskiy, A. Durandin, Y. Shim, J.H. Min, Y.C. Lee, V. Shafirovich, H. Mu, S. Broyde, N.E. Geacintov, The DNA damage-sensing NER repair factor XPC-RAD23B does not recognize bulky DNA lesions with a missing nucleotide opposite the lesion, DNA Repair (Amst). 96 (2020), 102985, https://doi.org/10.1016/j.dnarep.2020.102985.

[26] K. Nishimoto, H. Niida, C. Uchida, T. Ohhata, K. Kitagawa, A. Motegi, T. Suda, M. Kitagawa, HDAC3 is required for XPC recruitment and nucleotide excision repair of DNA damage induced by UV irradiation, Mol. Cancer Res. 18 (2020) 1367–1378, https://doi.org/10.1158/1541-7786.MCR-20-0214.

[27] C.T. Wong, D.H. Oh, Vitamin d receptor promotes global nucleotide excision repair by facilitating XPC dissociation from damaged DNA, J. Invest. Dermatol. 141 (2021) 1656–1663, https://doi.org/10.1016/j.jid.2020.11.033.

[28] R. Dip, U. Camenisch, H. Naegeli, Mechanisms of DNA damage recognition and strand discrimination in human nucleotide excision repair, DNA Repair (Amst). 3 (2004) 1409–1423, https://doi.org/10.1016/j.dnarep.2004.05.005.

[29] C. Ribeiro-Silva, M. Sabatella, A. Helfricht, J.A. Marteijn, A.F. Theil, W. Vermeulen, H. Lans, Ubiquitin and TFIIH-stimulated DDB2 dissociation drives DNA damage handover in nucleotide excision repair, Nat. Commun. 11 (2020) 1–14, https://doi.org/10.1038/s41467-020-18705-0.

[30] W. Sakai, M. Yuasa-Sunagawa, M. Kusakabe, A. Kishimoto, T. Matsui, Y. Kaneko, J. ichi Akagi, N. Huyghe, M. Ikura, T. Ikura, F. Hanaoka, M. Yokoi, K. Sugasawa, Functional impacts of the ubiquitin–proteasome system on DNA damage recognition in global genome nucleotide excision repair, Sci. Rep. 10 (2020), https://doi.org/10.1038/s41598-020-76898-2.

[31] Y. Zhang, I.K. Mandemaker, S. Matsumoto, O. Foreman, C.P. Holland, W.R. Lloyd, K. Sugasawa, W. Vermeulen, J.A. Marteijn, P.J. Galardy, USP44 stabilizes DDB2 to facilitate nucleotide excision repair and prevent tumors, Front. Cell Dev. Biol. 9 (663411) (2021), https://doi.org/10.3389/fcell.2021.663411. Apr.

[32] J.Y. Tang, B.J. Hwang, J.M. Ford, P.C. Hanawalt, G. Chu, Xeroderma pigmentosum p48 gene enhances global genomic repair and suppresses UV-induced mutagenesis, Mol. Cell 5 (4) (2000) 737–744, https://doi.org/10.1016/S1097-2765(00)80252-X.

[33] N. Goosen, Scanning the DNA for damage by the nucleotide excision repair machinery, DNA Repair (Amst). 9 (2010) 593–596, https://doi.org/10.1016/j.dnarep.2010.02.015.

[34] J.Q. Svejstrup, P. Vichi, J.M. Egly, The multiple roles of transcription/repair factor TFIIH, Trends Biochem. Sci. 21 (1996) 346–350, https://doi.org/10.1016/0968-0004(96)10046-3.

[35] M. Okuda, T. Ekimoto, J.I. Kurita, M. Ikeguchi, Y. Nishimura, Structural and dynamical insights into the PH domain of p62 in human TFIIH, Nucleic Acids Res. 49 (2021) 2916–2930, https://doi.org/10.1093/nar/gkaa1045.

[36] I.L. Hermanson-Miller, J.J. Turchi, Strand-specific binding of RPA and XPA to damaged duplex DNA, Biochemistry 41 (2002) 2402–2408, https://doi.org/10.1021/bi0112863.

[37] R.N.M.E.P.I.L.O, Y.S. Krasikova, Localization of xeroderma pigmentosum group A protein and replication protein A on damaged DNA in nucleotide excision repair, Nucleic Acids Res. 38 (2010) 8083–8094.

[38] C.J. Park, B.S. Choi, The protein shuffle: sequential interactions among components of the human nucleotide excision repair pathway, FEBS J. 273 (2006) 1600–1608, https://doi.org/10.1111/j.1742-4658.2006.05189.x.

[39] L. Staresincic, A.F. Fagbemi, J.H. Enzlin, A.M. Gourdin, N. Wijgers, I. Dunand-Sauthier, G. Giglia-Mari, S.G. Clarkson, W. Vermeulen, O.D. Schärer, Coordination of dual incision and repair synthesis in human nucleotide excision repair, EMBO J. 28 (2009) 1111–1120, https://doi.org/10.1038/emboj.2009.49.

[40] R.T. Hess, U. Schwitter, M. Petretta, B. Giese, H. Naegeli, Bipartite substrate discrimination by human nucleotide excision repair, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 6664–6669, https://doi.org/10.1073/pnas.94.13.6664.

[41] L.H.F.M, Albert A. van Zeeland, Annekevan Hoffen, Comprehensive series in photosciences. Compr. Ser. Photosciences, 2001, pp. 377–391, https://doi.org/10.1016/S1568-461X(13)60001-0.

[42] T. Ellenberger, A.E. Tomkinson, Eukaryotic DNA ligases: structural and functional insights, Annu. Rev. Biochem. 77 (2008) 313–338, https://doi.org/10.1146/annurev.biochem.77.061306.123941.

[43] J. Bartek, J. Lukas, DNA damage checkpoints: from initiation to recovery or adaptation, Curr. Opin. Cell Biol. 19 (2007) 238–245, https://doi.org/10.1016/j.ceb.2007.02.009.

[44] J.T. Zilfou, S.W. Lowe, Tumor suppressive functions of p53, Cold Spring Harb. Perspect. Biol. 1 (2009), https://doi.org/10.1101/cshperspect.a001883.

[45] A.B. Williams, B. Schumacher, p53 in the DNA-damage-repair process, Cold Spring Harb. Perspect. Med. 6 (2016) 1615–1624, https://doi.org/10.1101/cshperspect.a026070.

[46] T. DeVine, M.-S. Dai, Targeting the ubiquitin-mediated proteasome degradation of p53 for cancer therapy, Curr. Pharm. Des. 19 (2013) 3248–3262, https://doi.org/10.2174/1381612811319180009.

[47] C.L. Brooks, W. Gu, P53 regulation by ubiquitin, FEBS Lett. 585 (2011) 2803–2809, https://doi.org/10.1016/j.febslet.2011.05.022.

[48] M. Wade, Y.V. Wang, G.M. Wahl, The p53 orchestra: Mdm2 and Mdmx set the tone, Trends Cell Biol. 20 (2010) 299–309, https://doi.org/10.1016/j.tcb.2010.01.009.

[49] C.L. Brooks, W. Gu, New insights into p53 activation, Cell Res. 20 (2010) 614–621, https://doi.org/10.1038/cr.2010.53.

[50] M.L. Smith, p53 regulation of DNA excision repair pathways, Mutagenesis 17 (2002) 149–156, https://doi.org/10.1093/mutage/17.2.149.

[51] M.L. Smith, I.T. Chen, Q. Zhan, P.M. O'Connor, A.J. Fornace, Involvement of the p53 tumor suppressor in repair of u.v.-Type DNA damage, Oncogene 10 (1995) 1053–1059 (Accessed 19 February 2021), https://pubmed.ncbi.nlm.nih.gov/7700629/.

[52] J.M. Ford, P.C. Hanawalt, Li-Fraumeni syndrome fibroblasts homozygous for p53 mutations are deficient in global DNA repair but exhibit normal transcription-coupled repair and enhanced UV resistance, Proc. Natl. Acad. Sci. U. S. A. 92 (1995) 8876–8880, https://doi.org/10.1073/pnas.92.19.8876.

[53] J.M. Ford, P.C. Hanawalt, Expression of wild-type p53 is required for efficient global genomic nucleotide excision repair in UV-irradiated human fibroblasts,

J. Biol. Chem. 272 (1997) 28073–28080, https://doi.org/10.1074/jbc.272.44.28073.
[54] M.A. Wani, Q. Zhu, M. El-Mahdy, S. Venkatachalam, A.A. Wani, Enhanced sensitivity to anti-benzo(a)pyrene-diol-epoxide DNA damage correlates with decreased global genomic repair attributable to abrogated p53 function in human cells, Cancer Res. 60 (2000) 2273–2280 (Accessed 19 February 2021), https://pubmed.ncbi.nlm.nih.gov/10786695/.
[55] M.A. Wani, M.A. El-Mahdy, F.M. Hamada, G. Wani, Q. Zhu, Q.E. Wang, A.A. Wani, Efficient repair of bulky anti-BPDE DNA adducts from non-transcribed DNA strand requires functional p53 but not p21waf1/cip1 and pRb, Mutat. Res. - Fundam. Mol. Mech. Mutagen. 505 (2002) 13–25, https://doi.org/10.1016/S0027-5107(02)00107-0.
[56] Q. Zhu, M.A. Wani, M. El-Mahdy, A.A. Wani, Decreased DNA repair efficiency by loss or disruption of p53 function preferentially affects removal of cyclobutane pyrimidine dimers from non- transcribed strand and slow repair sites in transcribed strand, J. Biol. Chem. 275 (2000) 11492–11497, https://doi.org/10.1074/jbc.275.15.11492.
[57] B.J. Hwang, J.M. Ford, P.C. Hanawalt, G. Chu, Expression of the p48 xeroderma pigmentosum gene is p53-dependent and is involved in global genomic repair, Proc. Natl. Acad. Sci. U. S. A. 96 (1999) 424–428, https://doi.org/10.1073/pnas.96.2.424.
[58] S. Adimoolam, J.M. Ford, p53 and DNA damage-inducible expression of the xeroderma pigmentosum group C gene, Proc. Natl. Acad. Sci. U. S. A. 99 (2002) 12985–12990, https://doi.org/10.1073/pnas.202485699.
[59] K. Hastak, S. Adimoolam, N.D. Trinklein, R.M. Myers, J.M. Ford, Identification of a functional in vivo p53 response element in the coding sequence of the xeroderma pigmentosum group C gene, Genes Cancer 3 (2012) 131–140, https://doi.org/10.1177/1947601912456288.
[60] M.E. Fitch, I.V. Cross, J.M. Ford, p53 responsive nucleotide excision repair gene products p48 and XPC, but not p53, localize to sites of UV-irradiation-induced DNA damage, in vivo, Carcinogenesis 24 (5) (2003) 843–850, https://doi.org/10.1093/carcin/bgg031. May.
[61] X.W. Wang, H. Yeh, L. Schaeffer, R. Roy, V. Moncollin, J.M. Egly, Z. Wang, E. C. Friedberg, M.K. Evans, B.G. Taffe, V.A. Bohr, G. Weeda, J.H.J. Hoeijmakers, K. Forrester, C.C. Harris, p53 modulation of TFIIH–associated nucleotide excision repair activity, Nat. Genet. 10 (1995) 188–195, https://doi.org/10.1038/ng0695-188.
[62] T. Léveillard, L. Andera, N. Bissonnette, L. Schaeffer, L. Bracco, J.M. Egly, B. Wasylyk, Functional interactions between p53 and the TFIIH complex are affected by tumour-associated mutations, EMBO J. 15 (1996) 1615–1624, https://doi.org/10.1002/j.1460-2075.1996.tb00506.x.
[63] C.P. Rubbi, J. Milner, p53 is a chromatin accessibility factor for nucleotide excision repair of DNA damage, EMBO J. 22 (2003) 975–986, https://doi.org/10.1093/emboj/cdg082.
[64] A. Dutta, J.M. Ruppert, J.C. Aster, E. Winchester, Inhibition of DNA replication factor RPA by p53, Nature 365 (1993) 79–82, https://doi.org/10.1038/365079a0.
[65] Q.E. Wang, Q. Zhu, M.A. Wani, G. Wani, J. Chen, A.A. Wani, Tumor suppressor p53 dependent recruitment of nucleotide excision repair factors XPC and TFIIH to DNA damage, DNA Repair (Amst). 2 (2003) 483–499, https://doi.org/10.1016/S1568-7864(03)00002-8.
[66] H.B. Forrester, J. Li, D. Hovan, A.N. Ivashkevich, C.N. Sprung, DNA repair genes: alternative transcription and gene expression at the exon level in response to the DNA damaging agent, ionizing radiation, PLoS One 7 (2012), https://doi.org/10.1371/journal.pone.0053358.
[67] S.A. Amundson, A. Patterson, K.T. Do, A.J. Fornace, A nucleotide excision repair master-switch: p53 regulated coordinate induction of global genomic repair genes, Cancer Biol. Ther. 1 (2002) 145–149, https://doi.org/10.4161/cbt.59.
[68] L.F.Z. Batista, W.P. Roos, M. Christmann, C.F.M. Menck, B. Kaina, Differential sensitivity of malignant glioma cells to methylating and chloroethylating anticancer drugs: P53 determines the switch by regulating xpc, ddb2, and DNA double-strand breaks, Cancer Res. 67 (2007) 11886–11895, https://doi.org/10.1158/0008-5472.CAN-07-2964.
[69] L.F.Z. Batista, W.P. Roos, B. Kaina, C.F.M. Menck, p53 mutant human glioma cells are sensitive to UV-C-induced apoptosis due to impaired cyclobutane pyrimidine dimer removal, Mol. Cancer Res. 7 (2009) 237–246, https://doi.org/10.1158/1541-7786.MCR-08-0428.
[70] C. Barckhausen, W.P. Roos, S.C. Naumann, B. Kaina, Malignant melanoma cells acquire resistance to DNA interstrand cross-linking chemotherapeutics by p53-triggered upregulation of DDB2/XPC-mediated DNA repair, Oncogene 33 (2014) 1964–1974, https://doi.org/10.1038/onc.2013.141.
[71] Y.H. Wu, T.C. Wu, J.W. Liao, K.T. Yeh, C.Y. Chen, H. Lee, p53 dysfunction by xeroderma pigmentosum group C defects enhance lung adenocarcinoma metastasis via increased Mmp1 expression, Cancer Res. 70 (2010) 10422–10432, https://doi.org/10.1158/0008-5472.CAN-10-2615.
[72] J.Y. Krzeszinski, V. Choe, J. Shao, X. Bao, H. Cheng, S. Luo, K. Huo, H. Rao, XPC promotes MDM2-mediated degradation of the p53 tumor suppressor, Mol. Biol. Cell 25 (2014) 213–221, https://doi.org/10.1091/mbc.E13-05-0293.
[73] D. Nahari, L.D. McDaniel, L.B. Task, R.L. Daniel, S. Velasco-Miguel, E.C. Friedberg, Mutations in the Trp53 gene of UV-irradiated Xpc mutant mice suggest a novel Xpc-dependent DNA repair process, DNA Repair (Amst). 3 (2004) 379–386, https://doi.org/10.1016/j.dnarep.2003.03.001.
[74] G. Wang, L. Chuang, X. Zhang, S. Colton, A. Dombkowski, J. Reiners, A. Diakiw, X. S. Xu, The initiative role of XPC protein in cisplatin DNA damaging treatment-mediated cell cycle regulation, Nucleic Acids Res. 32 (2004) 2231–2240, https://doi.org/10.1093/nar/gkh541.
[75] L.J. Ko, S.Y. Shieh, X. Chen, L. Jayaraman, K. Tamai, Y. Taya, C. Prives, Z.Q. Pan, p53 is phosphorylated by CDK7-cyclin H in a p36MAT1-dependent manner, Mol. Cell. Biol. 17 (1997) 7220–7229, https://doi.org/10.1128/mcb.17.12.7220.
[76] H. Lu, R.P. Fisher, P. Bailey, A.J. Levine, The CDK7-cycH-p36 complex of transcription factor IIH phosphorylates p53, enhancing its sequence-specific DNA binding activity in vitro, Mol. Cell. Biol. 17 (1997) 5923–5934, https://doi.org/10.1128/mcb.17.10.5923.
[77] H.R. Rezvani, R. Rossignol, N. Ali, G. Benard, X. Tang, H.S. Yang, T. Jouary, H. De Verneuil, A. Taïeb, A.L. Kim, F. Mazurier, XPC silencing in normal human keratinocytes triggers metabolic alterations through NOX-1 activation-mediated reactive oxygen species, Biochim. Biophys. Acta - Bioenerg. 1807 (2011) 609–619, https://doi.org/10.1016/j.bbabio.2010.12.006.
[78] C.R. Sears, H. Zhou, M.J. Justice, A.J. Fisher, J. Saliba, I. Lamb, J. Wicker, K. S. Schweitzer, I. Petrache, Xeroderma pigmentosum group C deficiency alters cigarette smoke DNA damage cell fate and accelerates emphysema development, Am. J. Respir. Cell Mol. Biol. 58 (2018) 402–411, https://doi.org/10.1165/rcmb.2017-0251OC.
[79] A. Sassa, T. Fukuda, A. Ukai, M. Nakamura, M. Takabe, T. Takamura-Enya, M. Honma, M. Yasui, Comparative study of cytotoxic effects induced by environmental genotoxins using XPC- A nd CSB-deficient human lymphoblastoid TK6 cells, Genes Environ. 41 (2019), https://doi.org/10.1186/s41021-019-0130-y.
[80] N. Pajuelo-Lozano, J. Bargiela-Iparraguirre, G. Dominguez, A.G. Quiroga, R. Perona, I. Sanchez-Perez, XPA, XPC, and XPD modulate sensitivity in gastric cisplatin resistance cancer cells, Front. Pharmacol. 9 (2018), https://doi.org/10.3389/fphar.2018.01197.
[81] X. Teng, X.F. Fan, Q. Li, S. Liu, D.Y. Wu, S.Y. Wang, Y. Shi, M. Dong, XPC inhibition rescues cisplatin resistance via the Akt/mTOR signaling pathway in A549/DDP lung adenocarcinoma cells, Oncol. Rep. 41 (2019) 1875–1882, https://doi.org/10.3892/or.2019.6959.
[82] A. Sancar, L.A. Lindsey-Boltz, K. Ünsal-Kaçmaz, S. Linn, Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints, Annu. Rev. Biochem. 73 (2004) 39–85, https://doi.org/10.1146/annurev.biochem.73.011303.073723.
[83] F. D'Adda Di Fagagna, Living on a break: cellular senescence as a DNA-damage response, Nat. Rev. Cancer 8 (2008) 512–522, https://doi.org/10.1038/nrc2440.
[84] D.L. Cheo, L.B. Meira, R.E. Hammer, D.K. Burns, A.T.B. Doughty, E.C. Friedberg, Synergistic interactions between XPC and p53 mutations in double-mutant mice: neural tube abnormalities and accelerated UV radiation-induced skin cancer, Curr. Biol. 6 (1996) 1691–1694, https://doi.org/10.1016/S0960-9822(02)70794-X.
[85] M. Nollen, F. Ebert, J. Moser, L.H.F. Mullenders, A. Hartwig, T. Schwerdtle, Impact of arsenic on nucleotide excision repair: XPC function, protein level, and gene expression, Mol. Nutr. Food Res. 53 (2009) 572–582, https://doi.org/10.1002/mnfr.200800480.
[86] G. Giglia, N. Dumaz, C. Drougard, M.F. Avril, L. Daya-Grosjean, A. Sarasin, p53 Mutations in skin and internal tumors of xeroderma pigmentosum patients belonging to the complementation group C, Cancer Res. 58 (1998) 4402–4409 (Accessed 23 June 2021), https://pubmed.ncbi.nlm.nih.gov/9766670/.
[87] A. Sarasin, S. Quentin, N. Droin, M. Sahbatou, V. Saada, N. Auger, Y. Boursin, P. Dessen, A. Raimbault, V. Asnafi, J.L. Schmutz, A. Taïeb, C.F.M. Menck, F. Rosselli, L.D. La Rochelle, C. Robert, F.S. De Fontbrune, M. Sébert, T. Leblanc, P. Kannouche, S. De Botton, E. Solary, J. Soulier, Familial predisposition to TP53/complex karyotype MDS and leukemia in DNA repair-deficient xeroderma pigmentosum, Blood 133 (2019) 2718–2724, https://doi.org/10.1182/blood-2019-01-895698.
[88] A.A. Yurchenko, I. Padioleau, B.T. Matkarimov, J. Soulier, A. Sarasin, S. Nikolaev, XPC deficiency increases risk of hematologic malignancies through mutator phenotype and characteristic mutational signature, Nat. Commun. 11 (2020), https://doi.org/10.1038/s41467-020-19633-9.
[89] Q.E. Wang, C. Han, B. Zhang, K. Sabapathy, A.A. Wani, Nucleotide excision repair factor XPC enhances DNA damage-induced apoptosis by downregulating the antiapoptotic short isoform of caspase-2, Cancer Res. 72 (2012) 666–675, https://doi.org/10.1158/0008-5472.CAN-11-2774.
[90] C. Dominguez-Brauer, P.M. Brauer, Y.J. Chen, J. Pimkina, P. Raychaudhuri, Tumor suppression by ARF: gatekeeper and caretaker, Cell Cycle 9 (2010) 86–89, https://doi.org/10.4161/cc.9.1.10350.
[91] C. Dominguez-Brauer, Y.J. Chen, P.M. Brauer, J. Pimkina, P. Raychaudhuri, ARF stimulates XPC to trigger nucleotide excision repair by regulating the repressor complex of E2F4, EMBO Rep. 10 (2009) 1036–1042, https://doi.org/10.1038/embor.2009.139.
[92] M. M, S. CR, G. X, L. X, S. K, H. W, H. YY, Regulation of global genome nucleotide excision repair by SIRT1 through xeroderma pigmentosum C, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 22623–22628, https://doi.org/10.1073/PNAS.1010377108.
[93] G.J. Stout, M.A. Blasco, Telomere length and telomerase activity impact the UV sensitivity syndrome xeroderma pigmentosum C, Cancer Res. 73 (2013) 1844–1854, https://doi.org/10.1158/0008-5472.CAN-12-3125.
[94] N. Fayyad, F. Kobaisi, D. Beal, W. Mahfouf, C. Ged, F. Morice-Picard, M. Fayyad-Kazan, H. Fayyad-Kazan, B. Badran, H.R. Rezvani, W. Rachidi, Xeroderma pigmentosum C (XPC) mutations in primary fibroblasts impair base excision repair pathway and increase oxidative DNA damage, Front. Genet. 11 (2020) 1458, https://doi.org/10.3389/fgene.2020.561687.
[95] L.G. Aoude, V.F. Bonazzi, S. Brosda, K. Patel, L.T. Koufariotis, H. Oey, K. Nones, S. Wood, J.V. Pearson, J.M. Lonie, M. Arneil, V. Atkinson, B.M. Smithers, N. Waddell, A.P. Barbour, Pathogenic germline variants are associated with poor

survival in stage III/IV melanoma patients, Sci. Rep. 10 (2020), https://doi.org/10.1038/s41598-020-74956-3.

[96] J.C. Chen, J.C. Ko, Y.C. Taso, H.H. Cheng, T.Y. Chen, T.C. Yen, Y.W. Lin, Downregulation of xeroderma pigmentosum complementation group C expression by 17-allylamino-17-demethoxygeldanamycin enhances bevacizumab-induced cytotoxicity in human lung cancer cells, Pharmacology 106 (2021) 154–168, https://doi.org/10.1159/000509052.

[97] Y. Liu, X. Wang, W. Li, Y. Xu, Y. Zhuo, M. Li, Y. He, X. Wang, Q. Guo, L. Zhao, L. Qiang, Oroxylin A reverses hypoxia-induced cisplatin resistance through inhibiting HIF-1α mediated XPC transcription, Oncogene 39 (2020) 6893–6905, https://doi.org/10.1038/s41388-020-01474-x.