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Other Proteins Interacting with XP Proteins

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Introduction

Genetic defects in Nucleotide excision repair (NER) lead to the clinical disorder xeroderma pigmentosum (XP) in humans which is characterized by dramatically increased sensitivity to UV light and a predisposition to development of skin cancers.^{1,2} NER is a major mechanism of DNA repair in cells for the removal of a large variety of bulky DNA lesions induced by environmental genotoxic agents and chemicals. The molecular basis of XP has been attributed to mutations in eight XP proteins A-through-G that are required for NER-mediated removal of DNA damage and XP-variant (XPV). These seven proteins can be further sub-divided into three groups based on their activity in the NER process. XPA, XPC complexed with the HR23B protein, and XPE are required for sensing DNA damage and initiating the repair process. XPB and XPD components of the basal transcription factor TFIIH are helicases that create a DNA strand opening surrounding the adducted base(s). XPG and XPF are the endonucleases that perform the dual incisions to release the damaged strand and allow resynthesis using the non-damaged strand as a template.^{3–5} Protein-protein interactions are integral in the correct assembly of the pre-incision complex and for the positioning of the nucleases prior to incision. However, all seven XP proteins have been found to form complexes with proteins not directly involved in the NER mechanism. This chapter describes these non-NER protein and their interactions and discuss their effects on the XP proteins and genome repair and stability.

Finding DNA Damage: XPA, XPC, and XPE

Damage recognition, the first step of the NER process, is performed by three XP proteins: XPA, XPC, and XPE. These three proteins function to recognise DNA damage, recruit and assemble other repair factors, and initiate cell cycle control pathways. (delete “Of these proteins”), Deficiency in XPA results in the most severe XP phenotype.^{4,5} The protein interactions associated with this group of XP proteins is absolutely essential for efficient repair of DNA damage and cellular DNA damage responses.

XPC, a 106 kDa protein, is the primary damage recognition factor required for the global genome NER (GG-NER) repair pathway, one of the two subpathways of NER (the other is transcription-coupled NER or TC-NER).^{6,7} XPC forms a tight heterodimeric complex with HR23B, a 53 kDa ubiquitin ligase, and this interaction has been found to be indispensable for the stability of each protein as well as XPC’s damage recognition function.⁶ Due to the nature of the interaction between XPC and HR23B, this complex will be referred to as XPC for the remainder of this chapter. XPC has recently been shown to form a complex with centrin 2, a calmodulin protein involved in centrosome duplication;^{8,9} this occurs through direct interaction with XPC. Although this interaction is not required for NER *in vitro*, it forms a heterotrimeric complex with XPC and stimulates damage recognition, thus providing an extra sensitivity for DNA damage.⁸ In GG-NER, XPC also interacts with the XPE and XPA proteins to complete the damage recognition step as well as the basal

transcription factor TFIIH.^{5,7,10} In this case, XPE serves a similar role to that of centrin 2 to stimulate XPC's ability to recognize certain types of DNA damage. Unlike centrin 2, however, XPE is required for efficient GG-NER activity.¹¹ The involvement of XPC in GG-NER is regulated also by its sumoylation with the small ubiquitin-like SUMO-1 modifier; this modification is promoted by the recruitment of XPA to the damage site. Sumoylation of XPC is necessary to prevent UV-induced degradation of XPC by the 26S proteasome system¹² as well as the dissociation of XPC from the damage site.¹³ Once bound to damaged DNA, XPC recruits the basal transcription factor TFIIH through interaction with the p62 subunit of TFIIH, an interaction that serves to position TFIIH prior to opening the damage site.⁷ The XPC-TFIIH interaction also serves a role in linking GG-NER to the cell cycle checkpoint kinase Ataxia-Telangiectasia Mutated (ATM).¹⁴ This interaction requires the NER nuclease XPG, apparently to prevent apoptosis in the presence of certain DNA lesions.¹⁴ XPC also has been linked to the base excision repair (BER) pathway via an interaction with thymine DNA glycosylase (TDG). Although XPC is not a required factor for BER, the XPC-TDG interaction is believed to stimulate recognition of the damaged base by TDG.¹⁵

XPE (also known as DDB-2) is a 48kDa protein and is part of the heterodimeric UV-damaged DNA binding complex (UV-DDB) (see chapter 7). XPE interacts with DDB-1, a 178kDa protein, to form the UV-DDB damage recognition complex that stimulates the damage recognition step in GG-NER.¹⁶ XPE interacts with a variety of proteins to modulate cellular responses to DNA damage. Interactions between XPE and the CBP/p300^{17,18} and STAGA^{18,19} chromatin remodeling complexes also are critical for the efficient removal of damage by the GG-NER pathway. These complexes acetylate histones, thereby relaxing the local chromatin superstructures to allow access to the DNA for processes such as repair or transcription. This is supported by the finding that XPE associates with mono-ubiquitinated histone H2A following UV irradiation. This ubiquitinylation is a modification that leads to relaxing of chromatin structure.²⁰ In addition, XPE interacts with transcriptional cofactors, such as E2F1, to inhibit production of replication factors and arrest cell cycle progression.^{18,21} Along with its role in transcriptional repression, XPE interacts with the Cullin4-ROC1-COP9 signalsome, which is part of the E3 ubiquitin ligase complex.^{22,23} This pathway mediates 26S proteasome, degradation of ubiquitinated proteins, and the interaction with XPE may serve to modulate protein degradation in response to UV irradiation.^{18,24} Recently, XPE was found to interact with c-Abl tyrosine kinase and this interaction has been linked to modulation of Cullin4 targeting of XPE for degradation by the 26S proteasome following UV irradiation.²²

XPA, a 32 kDa zinc metalloprotein, is the sole recognition factor required for both GG-NER and TG-NER activities and is believed to play a role in verification of DNA damage.^{25,26} To date, the only known function for the XPA protein is in mediating NER and its protein interaction partners are limited primarily to factors required for damage removal.²⁵⁻²⁷ The primary XPA interaction occurs with the single-stranded DNA binding protein or replication protein A (RPA).^{5,27-29} Following UV irradiation, both XPA and RPA are recruited to the damage site via interactions with XPC and TFIIH and, once assembled, form a tight complex that stays associated with the damage site throughout processing.^{4,5} Rad14, the yeast counterpart of XPA, also forms a tight complex with Rad1-Rad10 nuclease, the yeast counterpart of XPF-ERCC1.³⁰ A recent *in vitro* study has suggested that the high affinity of XPA for the damage site may not be dependent on the damaged base but rather on the pre-incision DNA structures generated by local unwinding of the DNA surrounding the damage.³¹ Thus, XPA may play a structural role in maintaining the pre-incision DNA bubble and positions the remaining NER factors, particularly XPF-ERCC1,³⁰ for final incisions while RPA may protect the undamaged strand (which will be used as the template for re-synthesis following incisions) from nuclease attack.³²

Other XPA interacting proteins include ATR (ATM and RAD3-Related),³³ a DNA damage checkpoint kinase of the phosphoinositide 3-kinase-like kinase (PIKK) family, XAB1 (XPA-binding protein 1)^{34,35} and XAB2 (XPA-binding protein 2).^{36,37} The interaction of XPA with ATR may be responsible for the rapid translocation of XPA from the cytoplasm to the nucleus in response to UV irradiation as this activity is dependent on ATR and can be abolished using either ATR inhibitors or siRNA-mediated knockdown of the kinase.³³ Although the mechanism of the translocation remains unclear, it is possible that the XPA binding protein XAB1, a cytoplasmic GTPase, may be involved. XAB1 binds to XPA via the nuclear localization signal located in the N-terminal region of XPA and is believed to help shuttle XPA through the nuclear pore by virtue of GTP hydrolysis.^{34,35} However, this mechanism remains speculative. XPA also has been shown to be phosphorylated by ATR in a UV-irradiation dependent manner and abrogation of this event diminished cell survival against UV treatment, although the underlying mechanism is still unknown.³⁸

XPA interaction with XAB2 (XPA-binding protein 2) was identified by yeast-two hybrid screening.³⁴ XAB2 interacts with a variety of proteins including RNA Pol II and is active in mRNA splicing.^{36,37} While its role in NER is not quite clear, it is believed that it promotes TC-NER through its dual interaction between RNA Pol II and XPA. However, attempts to study this protein interaction *in vivo* using transgenic mice have proven difficult as deletion of XAB2 is embryonically lethal.³⁶

Preparing the Site: XPB and XPD

Following the initial damage recognition step, opening of the DNA surrounding the damaged base is accomplished by the basal transcription factor TFIIH.^{4,5} The helicase activity of TFIIH resides in two XP protein: XPB and XPD.³⁹ Although they play critical roles in NER, their activity also is critical for the transcriptional activation role TFIIH plays in mRNA synthesis. Therefore each helicase forms various protein-protein interactions that will be described in this section.

XPD, an 87 kDa protein, is a 5'→3' ATP-dependent helicase and serves as the dominant helicase in NER, although it plays only a minor role in transcription.²² XPD is part of the Cdk Activating Complex (CAK) component of TFIIH containing the additional subunits cdk7, cyclin H, and MAT1. XPD is bound to the CAK complex via an interaction with the coiled-coil region of the MAT1 subunit.⁴⁰ The CAK complex interacts with the TFIIH core complex via interaction of XPD with the N-terminal domain of p44 and therefore acts as a bridge between the two complexes.^{41,42} Besides its helicase activity and the structural role in binding together the TFIIH supercomplex, XPD has been shown to interact with hMMS19, a transcription cofactor found to stimulate estrogen receptor-mediated activation of the ER α promoter via stimulation of AF-1 activity.^{43,44} hMMS19 has been shown also to play a role in NER. However this function is still not completely understood.^{43,44} XPD, as well as XPB, interacts with the p53 apoptosis factor. Interaction with p53 has been demonstrated to inhibit the helicase activity of both XPD and XPB while reducing the instance of apoptosis. However, the mechanism of this protection is still unclear.⁴⁵⁻⁴⁹

XPB, a 90 kDa protein, is a 3'→5' ATP hydrolysis-driven helicase although it has much weaker activity compared to that of XPD.²² However, mutations in XPB are among the most rare in XP indicating XPB plays an extremely critical role in both NER and transcription.⁵⁰ In accordance with this observation, XPB interacts with a variety of different repair and transcription factors and it is these interactions, not XPB's helicase activity, that are critical for TFIIH activity. XPB is part of the TFIIH core complex and is positioned via interactions with the p62 p52, p44, and p8 subunits.⁵¹ Mutations in XPB are believed to disrupt these interactions, leading to the destabilization of TFIIH.^{50,51} The interaction between XPB and

p52 has been demonstrated as critical for XPB's role in promoter melting and defects in this interaction have serious consequences for transcription.⁵² Lin *et al.* demonstrated that XPB helicase activity also is modulated by the transcription factor TFIIE β subunit to promote transcription initiation by TFIIH.⁵³

Although the major NER helicase is XPD, modulation of XPB in NER is critical for the efficient removal of DNA lesions. Recently the XPB-p8 interaction has been shown to be important for NER.²² p8 stimulates the helicase activity of both XPB (through direct interaction) and XPD (via interaction through p44) to promote DNA strand opening, a step necessary for assembly of pre-incision complexes.²² The C-terminal of XPB can be phosphorylated by an as yet unidentified PP2A-related protein kinase and this phosphorylation is essential for the 5' incision by XPG.⁵⁴ Another critical interaction of XPB is that with hSUG1, a component of the 26S proteasome.^{55,56} Lommel *et al.* found that in yeast the XPB-SUG1 interaction modulated the degradation of Rad4, an XPC homologue, and yielded increased repair efficiency.⁵⁵ This, however, is not conclusive in XP as it is believed there is no proteolytic degradation of XPC by the 26S proteasome pathway.⁴

XPB, as well as XPD, have been shown also to directly associate with the recombination factor Rad52 and it is believed that this interaction serves to couple transcription with the error-free homologous recombinational repair pathway.⁵⁷ Recently, XPB has been demonstrated to associate with the p210BCR/ABL tyrosine kinase and this interaction promoted DNA repair by modulating the association of TFIIH with PCNA.⁵⁸ Although the exact mechanism of this modulation is unclear, it appears that XPB may modulate the role of TFIIH in homologous recombinational repair as well as in NER.

Cutting It Out: XPG and XPF

In NER, removal of the damaged oligonucleotides from the genome requires dual incisions to be made flanking the damage site. This process is accomplished by the remaining two XP proteins: XPG and XPF.^{4,5} Following opening of the damage site by TFIIH and dissociation of XPC/HR23B (in the case of GG-NER) the XPG and XPF nucleases are recruited to the damage site and positioned via protein-protein interactions with XPA, RPA, and components of the TFIIH complex.⁵ However, these two nucleases have also been reported to interact with other proteins in repair and transcription.

XPG, a 133 kDa protein, is a structure-specific nuclease that cleaves the damaged strand 3' to the damage site at the single-strand/double-strand DNA junction. XPG also serves a structural role in that helps in position the XPF/ERCC1 endonuclease for the 5' incision.^{59,60} The XPA/RPA and TFIIH complexes are required for recruitment and positioning of the nuclease prior to incision.⁶¹⁻⁶³ The p62 subunit of TFIIH contains a pleckstrin/phosphotyrosine homology domain that has been shown to specifically interact with the XPG nuclease.⁶⁴ Also, as described above, XPG interacts with the XPB helicase and the phosphorylation state of XPB modulates its nuclease activity.⁵⁴ Interaction of XPG with RPA is required for completing the incision.^{5,61} In addition, XPG shows a high degree of homology with the FEN-1 endonuclease, which is involved in processing of Okazaki fragments during DNA replication. Like FEN-1, XPG is able to associate with the replication elongation factor PCNA and this interaction is significant during re-synthesis of the excised region in NER.^{61,65} Recently it was reported that XPG could recognize and interact with RNA Pol II at stalled transcription bubbles.⁶ This finding may suggest a DNA damage recognition mechanism in which XPG initiates the recruitment of repair factors to remodel the stalled transcription bubble to repair lesions encountered by the elongating polymerase.⁶⁶ As with XPC, XPG also interacts with proteins from the BER pathway, in this case Nth1. Nth1 is a DNA glycosylase-AP lyase involved in repairing thymine glycol

lesions and other types of BER lesions. However, its affinity for the damaged base is greatly increased in the presence of XPG protein.^{67–69} In its interaction with Nth1, however, XPG does not incise the strand and serves only to stimulate Nth1.^{67–69}

XPF, a 103 kDa protein, is the second endonuclease required for NER. Like XPG, it is a structure-specific nuclease that recognizes the single-strand/double strand DNA junction 5' to the adducted base(s).⁷⁰ Together with its interaction partner, ERCC1, XPF cleaves the damaged strand in the unpaired region of the junction. XPF requires XPG and RPA to be bound to the substrate before it can be recruited and correctly positioned to make the cleavage.^{71,72} XPF also interacts with the homologous recombinational repair proteins Rad51 and Rad52 and is involved in the repair of interstrand crosslinks.^{73,74} Furthermore, XPF interacts with the FANCA, Msh2, and non-erythroid α -Spectrin α -SPII proteins, further demonstrating its role in the removal of interstrand crosslinks.^{75–78} A recently identified interesting role for XPF is its interaction with the telomere elongation factor TRF2. This factor is responsible for the conversion of telomeric TTAGGG repeats tracts to T-loop structures that protect the telomeres from inadvertent double-strand break repair. Also, it has been speculated that TRF2 performs a strand-break sensing role in the non-homologous end joining (NHEJ) repair pathway. Although it is still not clear what role TRF2 plays in repair of strand breaks, it is believed that its interaction with XPF promotes trimming of the ends in preparation for end joining.^{78,79}

11.5 Getting Past It: XPV

XPV (also known as pol η) is a 79 kDa protein and a member of the Y-Family DNA polymerases.⁷⁹ XPV has been identified as a member of the XP group of proteins although it does not participate in any NER subpathway.⁸⁰ Defects in XPV lead to development of the xeroderma pigmentosum variant disorder characterized by sensitivity to UV-irradiation despite an active NER repair pathway.^{79,80} The XPV polymerase is a trans-lesion polymerase that allows DNA synthesis to bypass UV photoproducts in an error-free manner^{81–83} and has been shown to physically interact with pol ι , another bypass polymerase.⁸² XPV associates with the replication machinery during DNA replication and interacts specifically with mono-ubiquitinated PCNA through two interaction sites on the polymerase.^{82–86} This interaction is promoted by the Rad18 ubiquitin ligase that forms a complex with PCNA and XPV.⁸⁷ Rad18 monoubiquitinates PCNA following replication-fork stalling which promotes polymerase switching from pol δ to XPV allowing trans-lesion synthesis past the damage site.^{83,87} Along with PCNA and Rad18, XPV also associates with Rev1 at stalled replication centers. Rev1, a deoxycytidyl transferase⁸⁹, is thought to play a structural role in providing a scaffolding for XPV to bypass certain lesions and this function is independent of its enzymatic activity.⁸⁸ XPV also is involved in the repair of interstrand crosslinks via direct interaction with Rad51⁹⁰. Rad51 recruits XPV to the D-loop recombination intermediate, a structure that XPV can use as a primer to initiate DNA synthesis.⁹⁰

Conclusions

It is clear that protein-protein interactions mediate the progression of nucleotide excision repair by promoting recognition of damaged DNA, recruitment of repair factors, and ultimately the removal of the damaged strand and re-synthesis of a new oligonucleotides patch. However, the XP proteins, required for NER, also are responsible for many other DNA metabolic processes, including repair, gene transcription and cell cycle control. Although much has been learned about how the XP proteins mediate the repair of damaged DNA, it is still unclear how repair affects and is affected by many cellular non-NER pathways. Continued research in how template DNA is handed off between competing

pathways via protein-protein interactions in response to DNA damage is required to fully understand how genome integrity is maintained.

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Table 11.1

Protein-protein interactions of the XP complementation groups Protein MW Function Interacting Proteins References

Protein	MW	Function	Interacting Proteins	References
XPA	32kDa	Damage Sensor	ATR: Cell-cycle Arrest Kinase	33,39
			RPA: single-strand DNA binding protein	4,5,27,28,91
			TFIIH: Transcription/Repair complex	4,5
			XAB1: GTPase	36,37
			XAB2: mRNA splicing	34,35
			XPF: Endonuclease	30
XPB	90kDa	3'→5' DNA Helicase	PP2A-related kinase: XPB phosphorylation	50
			p210BCR/ABL: tyrosine kinase	58
			p53: Transcription/apoptosis factor	47–49
			Rad52: Homologous recombination factor	57
			SUG1: Ubiquitin ligase	55,56
			TFIIE: Transcription Complex	53
			XPC: DNA damage sensor	7
			XPG: Endonuclease	51
			ATM: Cell-cycle arrest kinase	14
XPC	106kDa	Damage Sensor	Centrin2: Centrosome duplication	8,9,92
			Cullin4-ROC1: E3 Ubiquitin ligase components	93
			<i>N</i> -methylpurine DNA glycosylase: BER repair protein	15
			S5a: 26S proteasome component	12
			XPB: 3'→5' DNA Helicase	7
			XPE: DNA damage sensor	10
			XPG: Endonuclease	94
			hMMS19: Transcription Factor	43,44
XPD	87kDa	5'→3' DNA Helicase	p44: TFIIH component	42,95
			p53: Transcription/apoptosis factor	45,46
			MAT1: TFIIH component	40
XPE	48kDa	Damage Sensor	c-ABL: tyrosine kinase	22
			CBP/p300: Histone acetylase	17,18
			Cullin4-COP9: E3 Ubiquitin ligase components	18,24
				18,21
			E2F1: Transcription Factor	18,19
			STAGA: Histone acetylase	20
			uH2A: monoubiquitinated Histone H2A	10
			XPC: UV-DNA damage binding protein	
XPF	103kDa	Nuclease	αSPIIΣ: Nuclear structural protein	76,77
			FANC-A: Crosslink repair factor	76,77
			Msh2: Mismatch recognition factor	75,78

Protein	MW	Function	Interacting Proteins	References
XPG	133kDa	Nuclease	Rad51: Homologous recombination factor	73
			Rad52: Homologous recombination factor	74
			RPA: Single-strand DNA binding protein	72
			TRF2: Telomere elongation factor	96,97
			XPA: DNA damage recognition factor	30
			Nth1: DNA glycosylase	67–69
			PCNA: DNA replication elongation factor	61,65
			RNA Pol II: mRNA polymerase	66
			RPA: Single-strand DNA binding protein	61,72
			TFIIF: Transcription/Repair complex	59,61–64
XPV	79kDa	Y-Family DNA Polymerase	XPA: DNA damage recognition factor	61
			PCNA: DNA replication factor	83–86
			Pol η : Y-family DNA polymerase	82
			Rad18: Ubiquitin ligase	87
			Rad51: Homologous recombination factor	90
			Rev1: Deoxycytidyl transferase	88