



Published in final edited form as:

Gene. 2015 September 15; 569(2): 153–161. doi:10.1016/j.gene.2015.06.026.

The *ERCC1* and *ERCC4 (XPF)* genes and gene products

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Abstract

The *ERCC1* and *ERCC4* genes encode the two subunits of the ERCC1–XPF nuclease. This enzyme plays an important role in repair of DNA damage and in maintaining genomic stability. ERCC1–XPF nuclease nicks DNA specifically at junctions between double-stranded and single-stranded DNA, when the single-strand is oriented 5' to 3' away from a junction. ERCC1–XPF is a core component of nucleotide excision repair and also plays a role in interstrand crosslink repair, some pathways of double-strand break repair by homologous recombination and end-joining, as a backup enzyme in base excision repair, and in telomere length regulation. In many of these activities, ERCC1–XPF complex cleaves the 3' tails of DNA intermediates in preparation for further processing. ERCC1–XPF interacts with other proteins including XPA, RPA, SLX4 and TRF2 to perform its functions. Disruption of these interactions or direct targeting of ERCC1–XPF to decrease its DNA repair function might be a useful strategy to increase the sensitivity of cancer cells to some DNA damaging agents. Complete deletion of either *ERCC1* or *ERCC4* is not compatible with viability in mice or humans. However, mutations in the *ERCC1* or *ERCC4* genes cause a remarkable array of rare inherited human disorders. These include specific forms of xeroderma pigmentosum, Cockayne syndrome, Fanconi anemia, XFE progeria and cerebro-oculo-facio-skeletal syndrome.

Keywords

DNA repair genes; Human; Nucleotide excision repair; Ultraviolet light; Nucleases

1. Introduction

The human *ERCC1* and *ERCC4* genes encode proteins that associate to form a nuclease that participates in DNA repair and in maintaining chromosome stability. Because the gene products function as partners, they are considered together here. The product of the *ERCC4* gene is defective in complementation group F of the inherited human disorder xeroderma pigmentosum (XP-F). Consequently the *ERCC4* gene product is commonly referred to as XPF (Lehmann et al., 1994), and that terminology is used in this review. The ERCC1–XPF

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complex is a two subunit structure-specific nuclease. This nuclease cuts DNA specifically near junctions between single-stranded and double-stranded DNA, where the single strand departs 5' to 3' from the junction. ERCC1–XPF plays a central role in nucleotide excision repair (NER) of DNA, a process that removes DNA damage caused by ultraviolet (UV) radiation exposure and by DNA damaging agents that cause covalent helix-distorting adducts (Friedberg et al., 2006; Scharer, 2013). During NER, the ERCC1–XPF nuclease nicks on the 5' side of the damaged DNA strand, by cleaving an open “bubble” intermediate (Sijbers et al., 1996a; Evans et al., 1997a). ERCC1–XPF also processes 3' tails of DNA intermediates that occur in some double-strand break repair pathways. Further, ERCC1–XPF participates in repair of DNA interstrand crosslinks. The ERCC1–XPF protein complex is evolutionarily conserved in eukaryotes (Table 1).

Complete deletion of either *ERCC1* or *ERCC4* is incompatible with viability in mice or humans. As described below, mutations that impair *ERCC4* and *ERCC1* function cause several inherited human syndromes associated with increased sensitivity to DNA damage and developmental defects.

2. The *ERCC1* and *ERCC4* genes

2.1. The *ERCC1* gene

The human *ERCC1* was the first human DNA repair gene identified by molecular cloning. It was isolated by DNA-based correction of DNA repair-defective Chinese hamster ovary (CHO) cells. Several UV-radiation sensitive CHO cell lines, including lines designated 43-3B (Wood and Burki, 1982) and UV20 (Thompson et al., 1982), were assigned to UV-sensitive genetic complementation group 1 based on cell fusion experiments. Both of these cell lines are defective in forming incisions following UV irradiation (Thompson et al., 1982; Wood et al., 1982). After transfection of the cells with DNA from a human genomic DNA library, subclones could be isolated in which normal sensitivity to UV-radiation had been restored (Westerveld et al., 1984; Rubin et al., 1983). Specific human genomic restriction fragments were identified in such cellular subclones of 43-3B cells (Westerveld et al., 1984). The human gene was designated *ERCC1* as an abbreviation for “excision repair cross complementation group 1” because of the cross-species complementation of the human gene with CHO cells. The *ERCC1* cDNA was subsequently isolated by utilizing the human DNA present in complemented subclones (van Duin et al., 1986). The last exon of the *ERCC1* gene overlaps with the beginning of the *CD3E* gene, transcribed from the opposite DNA strand (van Duin et al., 1989). *CD3E* encodes a subunit of the T-cell receptor CD3 complex.

ERCC1 is located on human chromosome at 19q13.32 and comprises 10 exons spanning about 15 kilobases (kb) (van Duin et al., 1987). Four *ERCC1* transcript isoforms are annotated, arising from alternative splicing. The canonical transcript encoding functional ERCC1 protein is termed Isoform 1 in the UniProt database (or 202) and is called Isoform 2 in the NCBI Gene database. The other three transcript isoforms encode non-functional transcripts (van Duin et al., 1986). *ERCC1* is broadly expressed in mammalian tissues (Wu et al., 2009).

2.2. The ERCC4 gene

The *ERCC4* gene was isolated independently by two different strategies. One approach linked several findings. ERCC1 was known to be a homolog of the Rad10 protein from the budding yeast *Saccharomyces cerevisiae* (van Duin et al., 1986). This was a significant insight because Rad10 had been discovered to associate with yeast Rad1 protein, forming a nuclease involved in NER (Bardwell et al., 1993; Tomkinson et al., 1993). Biochemical experiments showed that ERCC1 functioned together in a complex with ERCC4 (Biggerstaff et al., 1993; van Vuuren et al., 1993). This led to the strong prediction that *ERCC4* was a homolog of *S. cerevisiae* *RAD1*. Further, it was found that the defect in CHO complementation group 4 cells was identical to the defect in cells from xeroderma pigmentosum group F (XPF) (Biggerstaff et al., 1993; van Vuuren et al., 1993). The cDNA encoding *ERCC4* was assembled from fragments homologous to *S. cerevisiae* Rad1 (Sijbers et al., 1996a). In a second approach, CHO cells in excision repair cross complementing group 4 were used, also defective in incision of DNA following UV radiation (Thompson et al., 1982). One such complementation group 4 cell line, UV41, was used to assign the *ERCC4* gene to human chromosome 16p13.1–p13.2 (Liu et al., 1993). The *ERCC4* gene was then isolated by complementation of UV41 cells with a human chromosome 16 cosmid library (Thompson et al., 1994). Using the *ERCC4* gene sequences, a functional *ERCC4* cDNA was assembled (Brookman et al., 1996).

ERCC4 is located on human chromosome 16p13.12 and consists of 11 exons spanning about 28.2 kb (Brookman et al., 1996). In human tissues, the broad tissue expression pattern of *ERCC4* is similar to that of *ERCC1* (Wu et al., 2009).

3. Biological functions of ERCC1-XPF

3.1. ERCC1-XPF in nucleotide excision repair

Nucleotide excision repair (NER) is a major mechanism for the repair of DNA damaged by chemicals causing helix-distorting covalent adducts and especially for the major UV photoproducts, the cyclobutane pyrimidine dimers and (6-4) photoproducts (Friedberg et al., 2006; Scharer, 2013). ERCC1–XPF is an essential structure-specific endonuclease for the repair of such damaged DNA in both replicating and non-replicating cells. ERCC1–XPF makes incisions on the damaged DNA strand on the 5' side of the open “bubble” intermediate formed during NER (Sijbers et al., 1996a; Evans et al., 1997a; Mu et al., 1996). In this process (Fig. 1), ERCC1–XPF acts in cooperation with the other protein factors required for the incision process in NER, which are XPC–RAD23B, XPA, RPA, TFIIH and XPG (Aboussekhra et al., 1995).

During global genomic nucleotide excision repair (GG-NER), initial distortions in DNA are recognized by XPC–RAD23B (Evans et al., 1997a; Sugasawa et al., 1998). Following this, TFIIH (containing XPB and XPD), XPA, RPA, XPG and ERCC1–XPF converge to form a preincision protein complex, which separates the DNA strands flanking the damaged site. Interactions of ERCC1 with XPA are functionally important within this complex (Volker et al., 2001; Li et al., 1994; Tsodikov et al., 2007; Tripsianes et al., 2007). Transcription-coupled NER (TC-NER) is initiated by the stalling of RNA polymerase II at a lesion on a

transcribed DNA strand (Hanawalt, 2002; Hanawalt and Spivak, 2008), after which other repair proteins including CSA, CSB, TFIIH, XPA and RPA are recruited to the damaged site. In both GG-NER and TC-NER, ERCC1–XPF makes an incision on the damaged DNA strand on the 5' side of the lesion, while XPG makes an incision on the 3' side of the lesion (O'Donovan et al., 1994).

The 5' incision and the 3' incisions occur nearly simultaneously during NER, with uncoupled incisions occurring occasionally on either side (Moggs et al., 1996; Gaillard and Wood, 2001). During the normal course of NER, ERCC1–XPF makes the 5' incision, a DNA repair polymerase initiates synthesis of a repair patch by copying the undamaged DNA strand, and a 3' incision is then made by XPG (Staresincic et al., 2009). In human cells, an incision fragment containing the damaged DNA is then released with a modal length of 27–29 nucleotides (Moggs et al., 1996; Bessho et al., 1997a; Huang et al., 1992).

3.2. Double-strand break repair

ERCC1–XPF-deficient cells are moderately more sensitive than normal to double strand break (DSB) inducing agents including ionization radiation produced by x-rays and γ -rays (Wood et al., 1983; Murray et al., 1995; Murray and Rosenberg, 1996; Ahmad et al., 2008). Following exposure to ionizing radiation, ERCC1–XPF-deficient mice and mouse fibroblasts show increased γ H2AX foci (a marker of DNA damage), as well as chromosomal abnormalities such as radial structures, gaps and breaks, which are consequences of DSBs (Ahmad et al., 2008). These data indicate that ERCC1–XPF has an important role in one or more pathways of DSB repair. The homologous Rad1–Rad10 nuclease in *S. cerevisiae* (Ivanov and Haber, 1995; Paques and Haber, 1999) plays a role in the single-strand annealing sub-pathway of homologous recombination. This pathway involves enzymatic processing that yields 3' DNA overhangs that must be removed to complete repair (Fishman-Lobell and Haber, 1992; Prado and Aguilera, 1995). In mammalian cells, ERCC1 is also required for the removal of long non-homologous ends in targeted homologous recombination (Adair et al., 2000). An ERCC1 defect similarly causes a failure to repair DNA intermediates during single-stranded annealing recombination (Sargent et al., 1997; Al-Minawi et al., 2008, 2009; Bennardo et al., 2008).

Non-homologous end-joining (NHEJ) mediated repair of DSB operates without requiring extensive homology for recombination (Mills et al., 2004). Yeast Rad1–Rad10 processes 3' ends during microhomology mediated end joining (Ma et al., 2003; McVey and Lee, 2008). Similarly, in mammalian cells, ERCC1–XPF plays a role in removing the 3' non-homologous ends of some double strand breaks during end-joining. This end joining involving ERCC1–XPF proceeds by an “alternate end-joining” pathway independent of the classical Ku70–Ku80 pathway (Ahmad et al., 2008; Bennardo et al., 2008). Immunoglobulin class-switching proceeds by end-joining pathways, and there is a modest reduction in class-switching in ERCC1-defective mouse B-cells (Schradler et al., 2004).

3.3. Interstrand crosslink repair

DNA interstrand crosslinks (ICLs) are challenging to repair because they obstruct DNA replication and transcription (Klein Douwel et al., 2014; Hodskinson et al., 2014). ERCC1

and XPF-deficient cells are exceptionally sensitive to agents that can form ICLs such as cisplatin, psoralen and mitomycin C (Wood, 2010). Cells defective in other NER genes are comparatively less sensitive to ICL-inducing agents (Andersson et al., 1996; Damia et al., 1996). This shows that ERCC1–XPF has an important role in ICL repair, independent of the NER pathway (Ahmad et al., 2008; Wood, 2010; Fisher et al., 2008; Rahn et al., 2010; Kuraoka et al., 2000). When a DNA replication fork encounters an ICL, a DSB can be formed by enzymatic action (Ahmad et al., 2008; Niedernhofer et al., 2001; Bergstralh and Sekelsky, 2008). XPF and ERCC1 mutants are reported to show defects in the incision or “unhooking” step of ICL repair (De Silva et al., 2000), as well as in the downstream processing of ICL-associated DSBs (De Silva et al., 2002). ERCC1–XPF can cleave 5' to an ICL in duplex DNA near the junction between single-stranded and double stranded DNA. Following this, it is capable of making a further cut on the other side of the ICL to generate a 4-mer crosslinked to DNA that may be an intermediate for the further processing (Kuraoka et al., 2000; Fisher et al., 2008).

ERCC1–XPF interacts with the SLX4 protein, during the processing of an ICL in cooperation with ubiquitinated FANCD2 (Klein Douwel et al., 2014). SLX4 acts as a scaffold protein during ICL repair. ERCC1–XPF binds to the N-terminal end of SLX4, enhancing action of the nuclease complex in mouse cells and in extracts from *Xenopus* eggs (Klein Douwel et al., 2014; Hodskinson et al., 2014). The mismatch recognition protein complex MSH2–MSH3 also binds to SLX4 (Svendsen et al., 2009; Kim et al., 2013), and there appear to be direct interactions between ERCC1 and MSH2–MSH3 (Lan et al., 2004).

There appear to be several different routes for ICL repair in mammalian cells; for example, some ICL repair can occur in the absence of DNA replication, as in non-dividing cells (Vasquez, 2010). In bacteria, a psoralen ICL (Van Houten et al., 1986) and a psoralen ICL directed by a triplex-forming oligonucleotide (Christensen et al., 2008) can be repaired by dual incision via the NER pathway. It is possible that this also occurs in mammalian cells. Finally, repair of the unhooked ICL may be completed by either homologous recombination using a new template or by TLS-mediated bypass and NER to remove an unhooked structure (Wood, 2010; Kuraoka et al., 2000; Deans and West, 2011). During ICL repair, ERCC1 may be regulated by USP45-dependent deubiquitination. ERCC1 binds to the USP45 deubiquitylase, and ERCC1 ubiquitination was increased in USP45 knockout cells (Perez-Oliva et al., 2015).

3.4. Base excision repair

Exposure of cells to reactive oxygen and nitrogen species damages the bases and the sugar-phosphate backbone of DNA. Some DNA glycosylases such as OGG1, NEIL1, and NTH1 can remove specific oxidized bases, and then cleave the resulting apurinic/aprimidinic (AP) site with an associated AP lyase activity. This leaves the 3' end with a non-hydroxyl group such as a deoxyribose phosphate. The 3' groups must be removed to allow complete repair. An AP nuclease (in mammalian cells, APEX1) normally acts to convert these 3' ends to a 3'-OH terminus. In *S. cerevisiae*, processing of such 3' ends can still occur in the absence of AP nuclease. Such backup processing is dependent on Rad1–Rad10 (Guillet and Boiteux, 2002). Similarly, mammalian ERCC1–XPF also can remove a 3'-phosphoglycolate

(produced by reactive oxygen species attack) from the 3' end of DNA in vitro (Fisher et al., 2011). ERCC1–XPF may therefore serve a backup role in processing of DNA damaged by reactive oxygen species in mammalian cells.

3.5. Maintenance of telomeres

ERCC1–XPF shows genetic interactions with the telomere maintenance protein TRF2. Mice overexpressing TRF2 are hypersensitive to UV radiation compared to normal mice. Chromosomes from these mice suffer telomere loss that is dependent on ERCC1–XPF (Munoz et al., 2005). On the other hand, ERCC1–XPF expression in TRF2-deficient cells causes increased chromosomal end fusions (Zhu et al., 2003). Mechanistically, ERCC1–XPF can cleave 3' overhangs from uncapped telomeres. This results in the shortening of the telomeres, together with premature aging in mice. ERCC1–XPF and TRF2 are associated via interaction with the SLX4 protein, and together they participate in regulation of telomere length (Munoz et al., 2005; Zhu et al., 2003; Wu et al., 2008; Wan et al., 2013). The balance between the expression of ERCC1–XPF and TRF2 may be critical for life expectancy and genomic stability.

4. Structural biochemical mechanism and interactions

The human ERCC1 protein has 297 amino acids and a molecular mass of 32,500 Da, while the *ERCC4*-encoded XPF protein comprises 916 amino acids, with a molecular mass of 104,000 Da. ERCC1–XPF functions as a complex to form an active endonuclease in DNA damage repair. The active nuclease domain residues are present in XPF, but XPF alone is not a nuclease. ERCC1 is necessary as a partner, serving as a critical DNA binding subunit. As a nuclease ERCC1–XPF does not cut double-stranded or single-stranded DNA. Instead, it cuts DNA specifically at junctions between single-stranded and double-stranded DNA, where the single strand departs 5' to 3' from the junction. Structures that are cleaved in this manner (with varying efficiencies) include stem-loop bubble substrates, substrates with splayed arms, flaps and protruding single arms (Fig. 1). These represent intermediate structures during many DNA transactions (O'Donovan et al., 1994; Bessho et al., 1997b; de Laat et al., 1998a; Evans et al., 1997b). ERCC1–XPF is the prototype for a family of structure specific-nucleases, which are related by structural and primary sequence similarity. In mammalian cells, members of this family include MUS81-EME1 and SLX4-SLX1, each of which has different and defined DNA substrate preferences (Hanada et al., 2006; Heyer, 2004).

ERCC1 contains a central domain interacting with DNA and proteins, a DNA-interacting helix–hairpin–helix (HhH) domain in the C-terminus, and a region at the N-terminus that is dispensable for some functions (Fig. 2). XPF consists of an N-terminal domain with distant homology to DNA helicases of superfamily 2, a central domain containing the nuclease active site, and a C-terminal HhH domain. The helicase similarity domain of XPF lacks catalytic residues that would confer ATP hydrolysis or nuclease activity, and it can be considered a disrupted helicase retaining only structural homology (Sgouros et al., 1999). ERCC1 and XPF have sequence similarity to one another in their central and nuclease domains, and in their HhH domains (Gaillard and Wood, 2001). It appears that the

mammalian ERCC1 gene arose in an ancient gene duplication event involving an ancestor of the ERCC4 gene.

The nuclease domain of XPF includes residues that coordinate a divalent cationic metal atom, and these residues are necessary for nuclease activity (Enzlin and Scharer, 2002). The corresponding homologous region of ERCC1 lacks these conserved metal-coordinating residues (Tsodikov et al., 2005). ERCC1 and XPF interact via their similar C-terminal helix–hairpin–helix domains (de Laat et al., 1998a,b; Tsodikov et al., 2005). In addition to dimerization, the HhH domains also contribute to DNA binding (de Laat et al., 1998c; Doherty et al., 1996; Su et al., 2012). The central domain of ERCC1 binds to single-stranded DNA with higher affinity than to double-stranded DNA (Tsodikov et al., 2005; McNeil and Melton, 2012). It has been proposed that the central domain of ERCC1 binds to single-stranded DNA, while the HhH regions of ERCC1 and XPF secure two splayed arms of DNA to test and insure a conformation allowing nuclease activity (Tsodikov et al., 2005) (Fig. 3). Structural studies by NMR indicate that the HhH2 domain of XPF binds to ssDNA, and the HhH2 domain of ERCC1 binds to dsDNA (Das et al., 2012).

A minimal complex consisting of N-terminally truncated ERCC1 beginning at residue 95 and N-terminally truncated XPF beginning at residue 656 can mediate some structure-specific cleavage of DNA (Tsodikov et al., 2005), showing that the N-terminal helicase-like domain of XPF is not absolutely required for the activity. However, the Arg153Pro substitution found in the XFE progeroid patient described below causes hypersensitivity to UV and ICL causing agents (Niedernhofer et al., 2006). This underlines that the conformation of the N-terminal region of XPF influences ERCC1–XPF activity.

Interactions with different protein partners are specific for of the pathway where ERCC1–XPF is involved. During NER, ERCC1 interacts with XPA (Li et al., 1994; Park and Sancar, 1994), while the N-terminal region of XPF binds to RPA. Further, RPA directly interacts with XPA. These interactions are necessary to target the ERCC1–XPF nuclease for specific action during NER (Li et al., 1994; Bessho et al., 1997b; McNeil and Melton, 2012; Matsunaga et al., 1996; Orelli et al., 2010). During ICL repair, ERCC1–XPF interacts with SLX4 (Klein Douwel et al., 2014; Hodskinson et al., 2014).

Formation of the ERCC1–XPF complex is also necessary to maintain stability of the two proteins (Gaillard and Wood, 2001; Sijbers et al., 1996b). When the individual subunits of ERCC1 and XPF are expressed separately, they self-aggregate in the absence of the other partner (Gaillard and Wood, 2001), a condition that would lead to proteolytic degradation in mammalian cells. Extracts of yeast *S. cerevisiae* Rad1 or Rad10 mutant cells can be complemented to nearly normal levels by introduction of the missing protein (Wang et al., 1993). However, this is not the case for human ERCC1 and XPF mutants (Gaillard and Wood, 2001). Effectively, XPF mutant cells are also ERCC1-deficient, and ERCC1 mutant cells are XPF-deficient (Gaillard and Wood, 2001; Bhagwat et al., 2009; Niedernhofer et al., 2007).

5. Disorders associated with ERCC1-XPF

Several human inherited disorders are associated with mutations in the *ERCC1* or *ERCC4* genes. As described below, these include xeroderma pigmentosum, Cockayne syndrome, Fanconi anemia, XFE progeria, and cerebro-oculo-facio-skeletal syndrome. Mouse models for ERCC1 and XPF deficiency are proving valuable in understanding these conditions.

5.1. Disorders associated with XPF

5.1.1. Xeroderma pigmentosum—A rare autosomal disorder, xeroderma pigmentosum (XP) is characterized by extreme sensitivity to sunlight, pigmentation abnormalities, and predisposition to skin cancer due to deficiencies in the NER pathway (Friedberg et al., 2006; Kraemer and DiGiovanna, 1993; Cleaver, 2005; Lehmann et al., 2011; DiGiovanna and Kraemer, 2012). Abnormalities include photosensitivity, cutaneous atrophy, cutaneous telangiectasia, actinic keratoses, and malignant skin neoplasms (Friedberg et al., 2006). Neurological abnormalities, observed in a minority of cases, include low intelligence, abnormal motor activity, areflexia, impaired hearing, abnormal speech, and microcephaly. Ocular abnormalities include conjunctival injection, corneal abnormalities, impaired vision, photophobia, and neoplasms. Eight complementation groups (XP-A to XP-G, and XP-V) have been classified.

XP-F, occurring less frequently overall than other XP cases, accounts for approximately 7% of reported cases in Japan (Kraemer and DiGiovanna, 1993). Severe ocular and neurological abnormalities are rare in the XP-F patients observed (Gregg et al., 2011). Missense mutations are present in at least one allele in all XP-F patients, none of which affect the nuclease activity of the enzyme (Gregg et al., 2011). Basal cell carcinomas, squamous cell carcinomas, and keratoacanthomas were found in several diagnosed XP-F patients (Sijbers et al., 1998a).

One case, not typical of other XP-F cases, is patient XP42RO. This patient had mild ocular photophobia and exhibited acute skin reactions upon exposure to sunlight (Sijbers et al., 1998a). Basal and squamous cell carcinomas appeared after twenty-seven years of age. Progressive neurologic symptoms emerged in his late forties, which is unusual for an XP-F patient. XP42RO was homozygous for a R799W point mutation, a mutation that has also been identified in at least eight other XP-F patients (de Laat et al., 1998c; Gregg et al., 2011) (Fig. 2).

5.1.2. XFE progeroid syndrome—A progeroid syndrome has been described resulting from a mutation in the *ERCC4* gene (Niedernhofer et al., 2006). The patient, XP51RO, exhibited symptoms resembling premature aging, profound crosslink sensitivity, and frequent sunburns. Many neurologic, hepatobiliary, musculoskeletal, and hematopoietic symptoms were present. This clinical presentation is distinct from xeroderma pigmentosum, Cockayne syndrome, or combined xeroderma pigmentosum–Cockayne syndrome. XP51RO cells harbor a homozygous C → G transversion affecting position 458 in *ERCC4*, yielding a R153P mutation at a conserved arginine (Table 2). The mutation is located between motifs II and III of the disrupted helicase domain in a leucine rich region which may be involved in protein–protein interactions (Tsodikov et al., 2005; Niedernhofer et al., 2006) (Fig. 2).

5.1.3. Fanconi anemia and Cockayne syndrome—Fanconi anemia (FA) is distinguished by bone marrow failure, predisposition to cancer, congenital malformations, hypersensitivity to crosslinking agents, and chromosome fragility. Seventeen genes have been identified as FA genes. Most recently *ERCC4* was identified as a FA gene, designated FANCF in that context (Bogliolo et al., 2013). Patient FA104 was diagnosed with a malformative syndrome indicating FA, and developed bone marrow failure when 2 years old. The *ERCC4* gene of patient FA104 contained a 5 bp deletion in exon 8 (c.1484_1488 delCTCAA), leading to a frameshift and premature stop codon, as well as a missense mutation in exon 11 leading to an Arg689Ser change (Fig. 2, Table 2). Lymphoblastoid cell lines from this patient were sensitive to mitomycin-C and melphalan, which is consistent with FA, but were not hypersensitive to topoisomerase I inhibitor camptothecin or PARP inhibitor KU58948. FA104 cells showed normal FANCD2 monoubiquitination and RAD51 foci formation (Bogliolo et al., 2013).

Patient FA1333 was diagnosed with FA at 5 years of age. Symptoms included various developmental defects and bone marrow failure (Bogliolo et al., 2013). A 28 bp duplication is present in exon 11 of the maternal allele and is predicted to encode for a truncated XPF that lacks the double helix–hairpin–helix domain involved in ERCC1 and DNA binding interactions (Fig. 2). A missense mutation resulting in Leu to Pro at residue 230 is present in the paternal allele, causing a mutation in the disrupted helicase domain (Fig. 2). FA1333 lymphoblastoid cell lines derived from this patient were not impaired in FANCD2 monoubiquitination or RAD51 foci formation. Cells were sensitive to mitomycin C and melphalan, but insensitive to camptothecin and KU58948 (Bogliolo et al., 2013).

Cockayne syndrome (CS) patients suffer from developmental defects, neurological abnormalities, and abnormal skin photosensitivity (Kashiyama et al., 2013). CS can be classified into three different groups, CS type I, CS type II, and CS type III, based on severity. Sunlight sensitivity is milder than that of XP cases and skin cancers are not found in CS. Most CS individuals have mutations in *ERCC8* (CSA) or *ERCC6* (CSB), resulting in defective TC-NER. *ERCC1* or *ERCC4* mutations have been reported in at least three CS cases where *ERCC6* and *ERCC8* function was normal (Kashiyama et al., 2013).

Patient XPCS1CD displayed many characteristics of CS, XP, and FA, with exceptional sensitivity to mitomycin C (Lehmann et al., 2011). Symptoms include various developmental defects, neurological defects, sunburns with minimal sun exposure, and abnormal bone marrow (Lehmann et al., 2011). XP/CS/FA patient XPCS1CD carried two *ERCC4* heterozygous point mutations, yielding Cys236Arg and Arg589Trp variants (Fig. 2).

Cockayne syndrome patient CS1USAU had two heterozygous mutations in *ERCC4*: a point mutation yielding Cys236Arg (also found in XPCS1CD) located in the SF2 disrupted helicase domain and an insertion resulting in premature stop codon Tyr577* (Kashiyama et al., 2013) (Fig. 2). Dermal fibroblasts isolated from the patient showed a reduction in RNA-synthesis activity, signifying a deficiency in TC-NER (Lehmann et al., 2011).

5.1.4. ERCC4 mouse models—In the cDNA of human patient XP23OS, an adenine insertion was detected leading to a frameshift mutation and ensuing stop codon that would

lead to a deletion of the C-terminal half of XPF (Table 2) (Tian et al., 2004; Matsumura et al., 1998). It was hypothesized that XP23OS may be homozygous for this mutation or that the other allele is transcriptionally repressed. The only marked symptom exhibited by this patient was photosensitivity of the skin. XPF mutant mice mimicking the XP23OS patient mutation were generated by engineering a stop codon in exon 8, resulting in truncation of XPF at residue 445 (Tian et al., 2004). Approximately 15 days after birth, the weight of homozygous mice was 27% of wild-type controls or heterozygous mutants. Homozygous *Ercc4* mutant mice died at approximately 3 weeks. Their organs appeared morphologically normal, yet significantly smaller (Tian et al., 2004). However, hepatocytes from homozygous mutant mice contained enlarged nuclei. This severe phenotype is similar to that of mice with inactivating mutations in *ERCC1*, as described below. It is possible that the relatively mild phenotype of the human XP23OS patient arose because the second XPF allele in this individual expressed a small amount of normal XPF protein, or XPF protein with a less debilitating mutation.

5.2. Disorders associated with ERCC1 mutations

5.2.1. Cerebro-oculo-facio-skeletal syndrome/Cockayne syndrome—Individuals diagnosed with cerebro-oculo-facio-skeletal syndrome (COFS) have been identified with defects in NER genes due to mutations in *ERCC6/CSB*, *ERCC2/XPD*, or *ERCC5/XPG* (Meira et al., 2000; Graham et al., 2001; Hamel et al., 1996). In addition, the first patient (165TOR) diagnosed with *ERCC1* deficiency suffered from COFS. This individual exhibited severe developmental failure, mild NER impairment, microcephaly, and other facial and skeletal abnormalities (Jaspers et al., 2007). *ERCC1* cDNA and genomic DNA from 165TOR cells harbors a C → T transition, yielding a premature Q158X termination mutation derived from the maternal allele (Fig. 2). AC → G transversion in the paternal allele results in a Phe to Leu mutation at residue 231, which lies within the XPF-interacting helix–hairpin–helix domain (Kashiyama et al., 2013). This residue is normally conserved as Phe or Tyr in mammals, fish, plants, and fungi.

Cockayne syndrome type II patient CS20LO exhibited a homozygous mutation in exon 7 of *ERCC1*, producing a F231L mutation, which was also observed in patient 165TOR (Fig. 2).

5.2.2. ERCC1 mouse models—Several mouse models have been generated to study the consequences of disrupting *Ercc1* function (Gregg et al., 2011). In one model (*Ercc1*^{tm1Dwm}), the last four exons are lacking due to a mutation in exon 5, producing a truncated *ERCC1* protein that is unable to bind XPF (Gregg et al., 2011; McWhir et al., 1993). This *Ercc1* mutation resulted in elevated p53 levels in liver, brain, and kidney in the perinatal period. Mice died before weaning and had liver nuclear abnormalities (McWhir et al., 1993). In another model (*Ercc1*^{tmJhjh}), a neomycin resistance cassette was inserted into exon 7, resulting in the truncation of the helix–hairpin–helix motif required for XPF interaction (Gregg et al., 2011; Weeda et al., 1997). Postnatal growth was severely retarded and the mice died at approximately 3 weeks. Hematopoietic cells undergo rapid turnover, leading to premature exhaustion of stem cell reserves in *Ercc1*-deficient mice. Mice lacking *ERCC1* also had musculoskeletal and nervous system defects, and impaired liver function (Niedernhofer et al., 2006; Gregg et al., 2011).

Mutational analysis has shown that NER and crosslink repair are mildly affected by the deletion of the last four amino acids of ERCC1, and that repair is severely impaired by the truncation of the last five or six residues (Sijbers et al., 1996b). Residues 293 to 297 are at the C-terminal border of the HhH XPF binding domain (de Laat et al., 1998c). Removal of the first 91 amino acids does not significantly impact ERCC1 function (Sijbers et al., 1996b). An *Ercc1* mutant mouse was generated containing a seven amino-acid carboxy-terminal truncation (*Ercc1*²⁹² or *Ercc1*⁻⁷) (Weeda et al., 1997). *Ercc1*⁻⁷ homozygous mutants were born at lower than expected Mendelian ratio, were severely runted, and had a reduced lifespan. *Ercc1*⁻⁷ mice in the FVB mouse strain background had a maximal age of 78 days (Weeda et al., 1997).

ERCC1-deficient mice exhibit many signs of accelerated aging. *Ercc1*^{-/-} mice express 10% of the ERCC1–XPF content found in wild-type mice (Goss et al., 2011). These mice have a maximum lifespan of 32 weeks, while exhibiting marked premature age-related changes throughout the animal. Osteoporosis and intervertebral disc degeneration occur in *Ercc1*^{-/-} mice, with disc height reduced by 20–30% in 20-week old *Ercc1*^{-/-} mice in comparison to wild type controls (Gregg et al., 2011; Vo et al., 2010). Disc height of *Ercc1*^{-/-} mice at 20 weeks was comparable to naturally aging 2-year old mice. *Ercc1*^{-/-} mice displayed an age-dependent loss of disc matrix proteoglycans, which are critical for counteracting spine compression. Loss of proteoglycans in these mice may be partially attributed to increased cell senescence and apoptosis, which are responses to DNA damage (Vo et al., 2010). *Ercc1*^{-/-} mice are also afflicted with peripheral neuropathy, a degenerative disorder often associated with aging (Goss et al., 2011). Nerve conduction studies revealed significant abnormalities in 20-week old *Ercc1*^{-/-} mice, and the mice exhibit loss of peripheral nerve fibers, abnormal myelin structures, and myelin degeneration. This indicates that these mice both spontaneously and prematurely acquire peripheral sensory and motor neuropathy. Due to the fact that *Ercc1*^{-/-} mice are deficient in multiple DNA repair pathways, these data support the concept that DNA damage may contribute to age related neurodegeneration (Goss et al., 2011). Gene expression analysis of XPF–ERCC1 deficient mice indicates increased cell death and antioxidant defenses, a shift towards anabolism and reduced growth hormone/insulin-like growth factor 1 signaling (Niedernhofer et al., 2006). Similar changes are seen in wild-type mice in response to chronic genotoxic stress, caloric restriction, or with aging.

6. ERCC1–XPF and cancer treatment

As expected, reduction of ERCC1–XPF protein by shRNA-mediated suppression sensitizes cells to killing by DNA crosslinking agents such as cisplatin derivatives (Arora et al., 2010), which are extensively used in treatment of breast, prostate, ovarian and other cancers. Thus a combination of ERCC1–XPF inhibition together with chemotherapy may be effective for the treatment of some cancers. For this reason, it has been important to identify antibodies that can be used for immunohistochemical identification of ERCC1 and XPF in formalin-fixed, paraffin embedded sections (Bhagwat et al., 2009; Smith et al., 2014). Several approaches have been proposed to disrupt the function of ERCC1–XPF complex (reviewed in (McNeil and Melton, 2012)). These include disruption of the dimerization of ERCC1 and XPF inhibition of XPF nuclease activity, and inhibition of the binding of ERCC1–XPF to DNA.

Disruption of protein–protein interactions is another possibility, targeting interactions between ERCC1 and XPA or between XPF and RPA, SLX4, or RAD52 (reviewed in (McNeil and Melton, 2012)). Cells defective in ERCC1–XPF are more sensitive than normal to inhibitors of the ATR protein (Mohni et al., 2014), and to inhibitors of poly(ADP-ribose) polymerase (Postel-Vinay et al., 2013). These observations might open additional possibilities for combination therapies.

It is possible that high expression of ERCC1–XPF could be associated with resistance to some DNA damaging drugs. Few studies have been performed with antibodies verified to recognize ERCC1–XPF specifically and uniquely, but better reagents are now available that could be used to quantify the expression of ERCC1–XPF in patients before the treatment with such drugs (Bhagwat et al., 2009; Smith et al., 2014). Levels of both the ERCC1 and the XPF proteins would have to be elevated in order to have any biological effect.

Acknowledgments

This review and the corresponding Gene Wiki article are written as part of the Gene Review a series resulting from a collaboration between the journal GENE and the Gene Wiki Initiative. The Wiki Initiative is supported by National Institute of Health (GM089820). Additional support for Gene Wiki Reviews is provided by Elsevier, the publisher of GENE. We thank our research group colleagues for comments on the manuscript. Research in RDW's laboratory was supported by National Institutes of Health (NIH) grants CA132840, CA09717 from the National Cancer Institute, the M.D. Anderson Research Trust and the Grady F. Saunders Ph.D. Distinguished Research Professorship. We also acknowledge funding from NIH Cancer Center Support Grant P30-CA016672 to the University of Texas MD Anderson Cancer Center.

Abbreviations

AP	apurinic/aprimidinic
ATP	adenosine triphosphate
cDNA	complementary deoxyribonucleic acid
CHO	Chinese hamster ovary
COFS	cerebro-oculo-facio-skeletal syndrome
CS	Cockayne syndrome
DSB	double strand break
FA	Fanconi anemia
GG-NER	global genome nucleotide excision repair
HhH	helix–hairpin–helix
ICL	interstrand crosslink in DNA
kb	kilobase
NER	nucleotide excision repair
NHEJ	non-homologous end joining
OB-fold	oligonucleotide/oligosaccharide binding fold, the basic structural unit of binding to single-stranded DNA

RPA	replication protein A
SF2	helicases of superfamily 2
shRNA	small hairpin ribonucleic acid
TC-NER	transcription coupled nucleotide excision repair
TFIIH	transcription factor II H
UV	ultraviolet
XP	xeroderma pigmentosum
γH2AX	H2A histone family, member X, phosphorylated at serine 139

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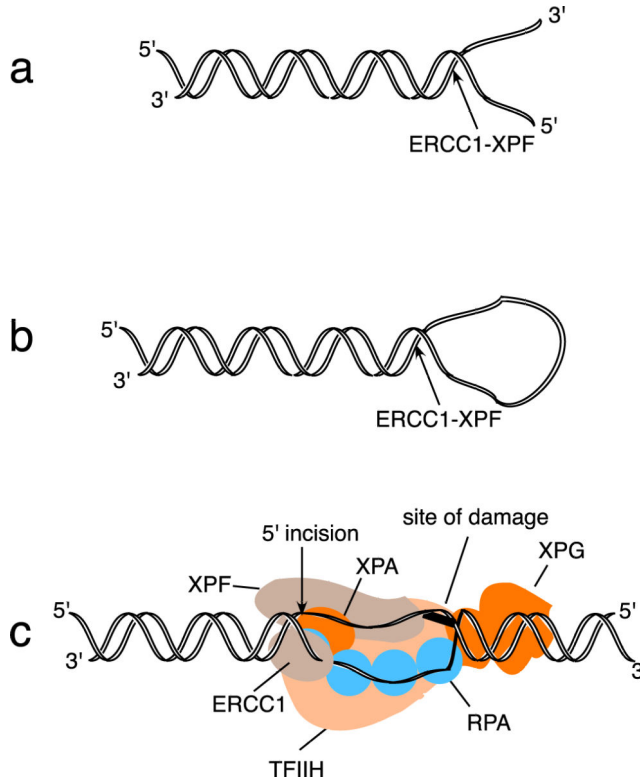


Fig. 1. Examples of DNA substrates for the ERCC1–XPF nuclease. a. ERCC1–XPF can cleave 3' ended tails from DNA by nicking within the duplex near the junction between double-stranded and single-stranded DNA. b. ERCC1–XPF can cleave a hairpin structure in DNA with the same polarity as in part a. c. The XPF–ERCC1 nuclease introduces the 5' incision during NER of an adduct on one strand. Shown here is the open preincision complex, containing TFIIH, XPA, RPA (which includes 4 active DNA-binding oligonucleotide binding (OB) fold domains among its 3 subunits), and XPG. The DNA strands have been separated in an ATP-dependent reaction, which creates a substrate for cleavage by ERCC1–XPF. The cleaved strand departs 5' to 3' from the junction, exactly as for the substrates as in parts a and b. The proteins and DNA are shown approximately to scale.

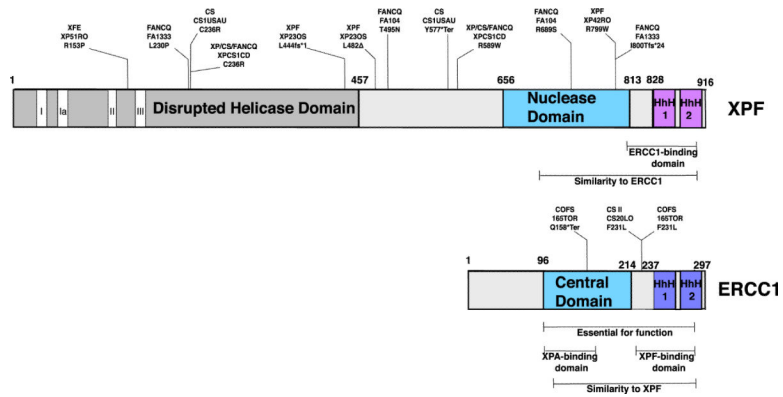


Fig. 2. Domain arrangement of the ERCC1 and ERCC4/XPF proteins, with examples of mutations found in human syndromes. XPF includes an N-terminal disrupted helicase domain and a nuclease domain. The central domain of ERCC1 shows similarity to the XPF nuclease domain, with critical nuclease residues absent. Both proteins have a C-terminal domain with two helix–hairpin–helix (HhH) motifs.

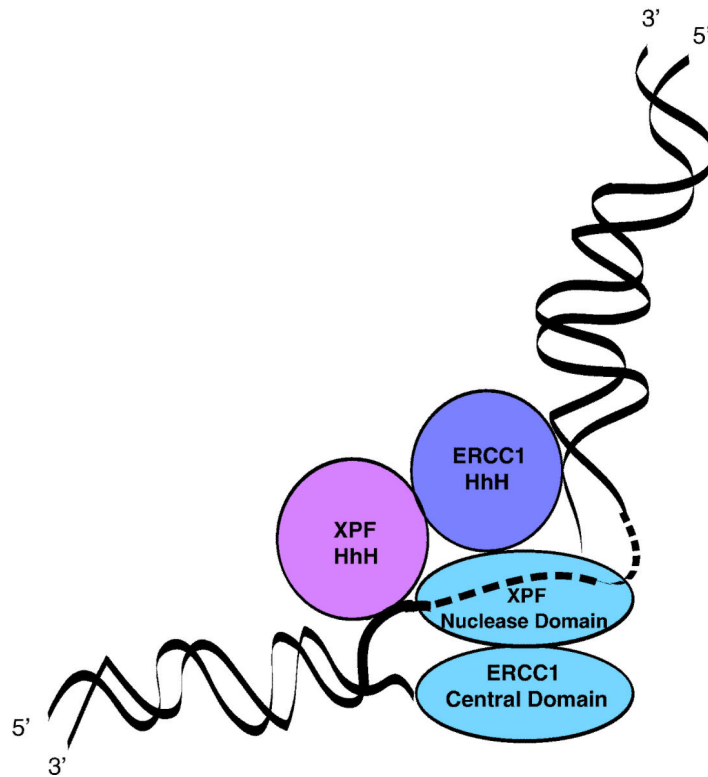


Fig. 3. ERCC1 and XPF interaction and binding of the complex with DNA (Friedberg et al., 2006). The central domain of ERCC1 binds to single-stranded DNA regions. The HhH regions of ERCC1 and XPF associate with one another, and bind to DNA to position the nuclease domain of XPF near the junction between single-stranded and double-stranded DNA.

Table 1

Orthologs of the *ERCC1* and *ERCC4* genes in some commonly studied eukaryotes.

Human	Mouse	<i>Drosophila</i>	<i>S. cerevisiae</i>	<i>S. pombe</i>
<i>ERCC1</i>	<i>Erc1</i>	<i>Erc1</i>	<i>RAD10</i>	<i>swi10</i>
<i>ERCC4</i>	<i>Erc4</i>	<i>Mei-9</i>	<i>RAD1</i>	<i>rad16</i>

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Table 2Examples of *ERCC1* and *ERCC4* mutations in human individuals with various inherited disorders.

Disorder	Patient	Ref.	Protein	Mutation	Protein change
FA	FA104	Bogliolo et al. (2013)	XPF	5 bp deletion exon 8	Thr495Asnfs*6
				Missense mutation exon 11	Arg689Ser
FA	1333	Bogliolo et al. (2013)	XPF	28 bp duplication in exon 11 of maternal allele	Ile800Thrfs*24
				Missense mutation in paternal allele	Leu230Pro
CS	CS1USAU	Kashiyama et al. (2013)	XPF	Exon 4 point mutation	Cys236Arg
				Exon 8 frameshift insertion, premature stop codon	Tyr577*
XP/CS/FA	XPCS1CD	Kashiyama et al. (2013)	XPF	Heterozygous point mutation	Cys236Arg
				Heterozygous point mutation	Arg589Trp
XFE progeroid	XP51RO	Niedernhofer et al. (2006)	XPF	Point mutation	Arg153Pro
XP	XP23OS	Matsumura et al. (1998)	XPF	1 bp insertion yielding a frameshift at 444 and stop at 482	Lys444 and 482*
XP	XP42RO	Sijbers et al. (1998b)	XPF	Point mutation	Arg799Trp
COFS	165TOR	Jaspers et al. (2007)	ERCC1	Point mutation (Maternal allele)	Gln158*
				Point mutation (Paternal allele)	Phe231Leu
CS type II	CS20LO ⁽¹⁰³⁾	Kashiyama et al. (2013)	ERCC1	Homozygous mutation, exon 7	Phe231Leu

* indicates that the mutation produces a termination codon, sometimes with a frameshift (fs) resulting in the indicated number of amino acid residues before termination.