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Nucleotide excision repair deficient mouse models and neurological disease

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Abstract

Nucleotide excision repair (NER) is a highly conserved mechanism to remove helix-distorting DNA base damage. A major substrate for NER is DNA damage caused by environmental genotoxins, most notably ultraviolet radiation. Xeroderma pigmentosum, Cockayne syndrome and trichothiodystrophy are three human diseases caused by inherited defects in NER. The symptoms and severity of these diseases vary dramatically, ranging from profound developmental delay to cancer predisposition and accelerated aging. All three syndromes include neurological disease, indicating an important role for NER in protecting against spontaneous DNA damage as well. To study the pathophysiology caused by DNA damage, numerous mouse models of NER deficiency were generated by knocking-out genes required for NER or knocking-in disease-causing human mutations. This review explores the utility of these mouse models to study neurological disease caused by NER deficiency.

Keywords

neurodegeneration; demyelination; endogenous damage

Introduction

Nucleotide excision repair

Nucleotide excision repair (NER) is a highly conserved multi-step pathway that removes helix-distorting DNA lesions from the genome (Figure 1). Sites of DNA damage are identified by NER in one of two ways, depending on the location of the lesion in the genome. Helix-distorting lesions anywhere in the genome are recognized by XPC in global genome NER (GG-NER). Damage recognition is facilitated HR23B or its homolog HR23A, which stabilize XPC [1,2]. Many of the DNA lesions that are substrates for NER are caused by environmental genotoxins. For instance, UV-induced 6-4 photoproducts and cyclobutane pyrimidine dimers are repaired by NER. Thus a hallmark feature of NER-deficiency is exquisite photosensitivity. A second protein complex DDB (comprised of DDB1 and DDB2/XPE) specifically facilitates recognition UV lesions by XPC-HR23B [2].

Damage to bases on the transcribed strand of a gene, which block transcription, triggers transcription-coupled NER (TC-NER). CSA, CSB and XAB2 facilitate TC-NER by stabilizing RNA polymerase II near the site of damage [3]. Once the lesion is identified, GG-NER and

TC-NER have a common excision mechanism. The multi-protein complex TFIIH, which is a basal transcription factor, is recruited to the site of damage through interactions with XPC-HR23B or CSA and CSB. XPG binds TFIIH and is critical for maintaining the structure of this multi-subunit complex [4]. Defects in three of the ten subunits of TFIIH (XPB, XPD and TTDA) cause photosensitivity [5], directly implicating them in NER. The XPB and XPD subunits are 3'-5' and 5'-3' helicases, respectively, and unwind the DNA around the lesion. Subsequently, XPA and RPA are recruited to the site and help stabilize the open structure [6]. XPA also facilitates recruitment of ERCC1-XPF nuclease, which incises the damaged strand of DNA 5' to the lesion, at the juncture between double-strand and single-strand DNA of the open complex. XPG makes the 3' incision. The lesion is thus excised in a 24-27 base single-stranded oligonucleotide. This leaves behind a single-strand gap that is filled by the replication machinery consisting of polymerase δ and ϵ , PCNA, RPA and RFC. The DNA backbone is sealed by DNA ligase I, restoring the original integrity of the DNA.

XPC, HR23B, DDB1 and DDB2 are proteins specifically required for GG-NER. CSA, CSB and XAB2 are required only for TC-NER. Defects in the two subpathways can be distinguished by measuring the cellular response to UV irradiation. Defects in GG-NER specific factors or proteins required for damage excision in NER result in reduced unscheduled DNA synthesis (UDS). UDS refers to non-S phase DNA polymerization. After UV irradiation of cells, it is a direct measure of gap-filling DNA synthesis in NER. Defects in proteins required for TC-NER do not affect UDS. However, cells defective in TC-NER have impaired recovery of RNA synthesis following exposure to UV, relative to cells defective in GG-NER.

Absence of GG-NER leads to the accumulation of DNA damage and as a consequence mutations and a cancer predisposition [7]. In contrast, defects in TC-NER lead to stalled transcription which is cytotoxic, causing very different sequelae at the organism level. There are no TC-NER-specific factors, because CSB, CSA and XAB2 appear to be required for transcription itself, making it difficult to determine to what extent TC-NER protects against disease.

Diseases caused by inherited defects in nucleotide excision repair

Inherited defects in NER cause three human syndromes with striking differences in symptoms and survival. Xeroderma pigmentosum (XP) is characterized by photosensitivity, hyperpigmentation and ichthyosis (dry scaly skin) in sun exposed areas, a >1000-fold increased risk of basal and squamous cell carcinomas and melanomas of the skin and eyes, and a 10-fold increased risk of non-cutaneous tumors [8]. There are seven complementation groups of XP, corresponding to defects in XPA to G. The severity of symptoms is for the most part determined by the nature of the mutation and the extent to which the mutation affects NER (UDS). Thus XP-C patients, missing only GG-NER, tend to have milder disease than XP-A patients, defective in XPA protein which is required for all NER. Approximately 20% of XP patients develop progressive neurologic symptoms that can emerge as early as at birth or as late as adulthood [9]

Cockayne syndrome (CS) is caused mutations in *CSA*, *CSB*, *XPB*, *XPD* or *XPG*. Symptoms include postnatal growth retardation, delayed psychomotor development, cachexia, microcephaly, mental retardation, joint contractures, ataxia and abnormal gait, hypogonadism, muscle atrophy, cataracts, osteopenia, dental caries, photosensitivity and a prematurely aged appearance [10]. There are three clinical subtypes of CS: severe infantile, childhood (in which patients are normal at birth but develop rapidly progressive growth defects and premature aging symptoms), and adult (in which the same symptoms develop in childhood but progress more slowly) [11]. Patients with trichothiodystrophy have all of the classic features of CS plus cutaneous symptoms including brittle hair and nails and ichthyosis (dry, scaly skin). TTD is caused by mutations in TFIIH subunits (*XPB*, *XPD* or *TTDA*) leading to destabilization or

dysfunction of the transcription factor [5]. The cutaneous symptoms are caused by impaired transcription of skin-specific genes [12]. In rare instances there are patients with combined XP and CS, due to mutations in *XPB*, *XPD* or *XPG*, and combined XP and TTD caused by mutations in *XPB* or *XPD*.

Many proteins required for NER have additional functions distinct from this repair mechanism (Table I and elaborated below). This complicates interpretation of disease phenotypes. However, to date, XPC has only been implicated in GG-NER and XPA only as a core protein in NER. Thus phenotypes caused by mutations in these genes can be interpreted to be the direct consequence of absence of GG-NER or NER.

Neurological disease in xeroderma pigmentosum

Neurological disease is progressive in XP and symptoms include loss of fine motor control, dementia, choreoathetosis, ataxia, unsteady gait, spasticity, rigidity, hyporeflexia, loss of hearing, laryngeal dystonia and dysarthria, dysphagia and peripheral sensory axonal neuropathy [9,13]. Neuropathological findings include microcephaly, cerebral cortical atrophy and enlarged ventricles. The root cause is progressive neurodegeneration in the cerebral cortex, basal ganglia, cerebellum, brain stem, corticospinal tract, cochlea, dorsal root ganglia and peripheral nerves [9,13,14]. Loss of neurons appears to be due to apoptotic cell death as a consequence of unrepaired spontaneous DNA damage [15]. Although there is progressive loss of myelinated fibers in peripheral nerves, myelination itself is not affected [16]. Glial cells also appear to be unaffected [15]. Neurological disease can emerge at any age in XP from the first to fourth decade of life [14]. The age at onset of neurological disease corresponds reasonably well with the extent of the DNA repair defect [9].

The majority of XP patients with neurologic symptoms are from complementation group A (XP-A). Neurologic involvement is also seen in some XP-B and XP-D patients [16]. Milder, adult onset neurologic impairment may be seen in XP-C and XP-F patients [17,18]. Neurologic disease has not been reported in XP-E(DDB2) patients [19].

Neurological disease in Cockayne syndrome and trichothiodystrophy

Neurologic defects in CS include postnatal growth failure of the brain leading to microcephaly, progressive dementia, mental retardation, spasticity, ataxia, progressive hearing loss and visual impairment [11,20,21]. Neuropathological findings in the central nervous system include atrophy of the white matter, enlarged ventricles, tigroid leukodystrophy (patchy degeneration of myelin) in the cerebral cortex, reactive gliosis, calcifications in the basal ganglia and atherosclerosis. There is also a demyelinating peripheral neuropathy, leading to neurogenic muscular atrophy. Loss of hearing is caused by degeneration of the organ of Corti, spiral and vestibular ganglia. Loss of vision is caused by atrophy of the optic nerve, retina, iris and ciliary body. Apoptotic cell death of granule cells and loss of Purkinje cells in the cerebellar cortex is seen in some CS patients, similar to XP [15]. Growth retardation with microcephaly, cataracts and brain mineralization can begin *in utero* (severe infantile CS) or symptoms may not emerge until childhood and then progress rapidly (classic CS) or very slowly (mild CS). Neurological disease in TTD is identical to CS.

Mouse Models of NER Defects and Their Neurological Disease

GG-NER

Xpc—XPC appears to function exclusively in NER, and more specifically in GG-NER. Thus genetic deletion of *Xpc* in the mouse reveals the biological significance of GG-NER. *Xpc*^{-/-} mice are viable, but have a reduced lifespan [22] and propensity for spontaneous tumors [23]. *Xpc*^{-/-} mice do not have obvious neurological abnormalities at least in the first year of life

[24,25] (Table I). This is in contrast to XP-C patients, who may have mild, adult onset neurologic symptoms [17]. Subtle neurological deficits are difficult to detect in mice and require specialized behavioral and electrophysiological tests, thus may have been overlooked in *Xpc*^{-/-} mice. Nevertheless, the fact that neurological disease is mild (or absent) in XP-C patients and *Xpc*^{-/-} mice indicates that GG-NER makes a relatively small contribution to the preservation of neurological function in mammals.

Interestingly, deletion of p53 leads to neural tube defects in mouse embryos [26,27]. Simultaneous deletion of XPC and p53 in the mouse (*Xpc*^{-/-};*p53*^{-/-}) causes a significant increase in the frequency of exencephaly, relative to *p53*^{-/-} mice [28]. This demonstrates that spontaneous DNA damage, normally repaired by GG-NER, can negatively impact development of the central nervous system.

hHR23A and hHR23B—HR23B forms a stable complex with XPC and facilitates GG-NER in vitro [1]. HR23A, a homolog in mammals, is redundant for this function. Deletion of HR23B in the mouse causes death in late embryonic development (>E15.5), demonstrating that HR23B has function(s) distinct from GG-NER [29]. Ten percent of *mHR23B*^{-/-} mice do survive and can live up to 1 year. These mice display growth retardation, cachexia, craniofacial dysmorphology and infertility [29]. A fraction of the mice are reported to have abnormal behavior suggesting involvement of the nervous system, although analysis is incomplete [29].

In contrast, deletion of HR23A in the mouse does not impact viability or lifespan and *mHR23A*^{-/-} mice appear normal to at least 18 mths of age [30]. Simultaneous deletion *mHR23A* and *mHR23B* causes early embryonic lethality (E8.5). These data demonstrate that HR23A is unable to compensate for all of the functions of HR23B. Both HR23 proteins contain a ubiquitin-like domain and two ubiquitin-associated domains [31], which are characteristic of proteins that chaperone ubiquitylated proteins to the proteasome for degradation [32]. Perturbation of protein degradation is strongly linked to numerous pathologies, in particular neurodegeneration [33,34]. Thus it appears likely that *mHR23B*^{-/-} mice will prove to have neurological disease, but not due to defective GG-NER.

DDB1 and DDB2—DDB, a complex of DDB1 and XPE/DDB2, binds UV damaged DNA with high affinity and is implicated in GG-NER specifically of UV photolesions. Each of the proteins also has functions distinct from NER and from one another. DDB1 is part of the Cullin 4A E3 ubiquitin ligase complex along with either DDB2 or CSA [35]. This complex binds damaged DNA and ubiquitylates DDB2- leading to its degradation, and XPC- leading to its stable association with DNA and promoting GG-NER [36]. DDB1-Cul4A also targets CSB for proteasomal degradation in TC-NER, in a CSA-dependent manner, promoting RNA synthesis recovery after DNA damage [37]. Other substrates for the DDB1-Cul4A complex include histones and proteins that regulate cell cycle progression. Homozygous deletion of DDB1 in the mouse causes early embryonic lethality [38]. If DDB1 is deleted only in the CNS, mice die uniformly within 24 hrs of birth [38]. Neuropathological findings include microcephaly, enlarged ventricles, extensive hemorrhaging and loss of brain architecture. This is due to apoptosis of proliferating neuronal progenitor cells in the developing embryo. The fact that DDB1, but not NER itself, is required for brain development indicates that this profound neuropathology in the absence of DDB1 is due to the loss of a function of this protein distinct from its role in NER.

In addition to interacting with the Cul4A complex, DDB2 acts as a transcriptional activator via an interaction with E2F1 and controls p53-dependent apoptosis in response to UV irradiation [39]. Deletion of *Xpe/Ddb2* in the mouse causes susceptibility to UV-induced skin carcinogenesis [39,40]. This is similar to *Xpa*^{-/-} and *Xpc*^{-/-} mice and consistent with a defect

in GG-NER of UV lesions. *Ddb2*^{-/-} mice also have a reduced lifespan and a predisposition to spontaneous tumors [40]. A different spectrum of spontaneous solid tumors is seen in *Xpc*^{-/-} mice [22]. Thus it is not clear if this tumor suppressor activity of DDB2 is attributable to a role in GG-NER of spontaneous DNA lesions or loss of another function of the protein. Neurological symptoms have not been reported in *Ddb2*^{-/-} mice or in XP-E patients [19].

Core NER

Xpa—XP-A patients with mutations that severely affect NER can have profound neurological disease. In stark contrast, no neuropathology was reported in *Xpa*^{-/-} mice [41,42]. However, subtle defects may exist based on the observation that *Xpa*^{-/-} mice experienced delayed neuromotor recovery and cognitive deficits following experimental brain trauma [22]. Further examination of *Xpa*^{-/-} mice with newer imaging techniques and behavioral studies is warranted.

Ercc1 and Xpf—ERCC1-XPF nuclease is essential for NER [43]. However, mammalian cell lines defective in ERCC1-XPF are hypersensitive to crosslinking agents and ionizing radiation compared to cells from other XP complementation groups ([44] and Niedernhofer unpublished data). This reveals a role for ERCC1-XPF in the repair of DNA interstrand crosslinks [45,46] and double-strand breaks [47], distinct from its function in NER. This complicates interpretation of mouse and patient phenotypes.

Deletion of *Ercc1* in the mouse causes dramatically accelerated aging of multiple organ systems and death by 4 weeks of age [44]. There is only one patient reported with a mutation in *Ercc1* [48]. The patient had severe growth and development delay, including microcephaly, beginning *in utero*, consistent with cerebro-oculo-facio-skeletal syndrome. Imaging revealed hypoplasia and decreased foliation of the cerebellum. Similar defects occur in *Ercc1*^{-/-} mice [49] and are accompanied by progressive dystonia, tremors and ataxia [44,50]. Presumably, the same occurs in *Xpf*^{-/-} mice [49], which appear to be a phenocopy of *Ercc1*^{-/-} mice.

Mutations in *hXPF* are typically associated with mild XP [18]. However, if protein expression is severely reduced in humans, this can cause a progeroid syndrome with symptoms remarkably similar to *Ercc1*^{-/-} mice [44]. Neurological symptoms in this progeroid *Xpf* patient included microcephaly, cognitive deficits, hearing loss, visual impairment, loss of fine motor control, ataxia, poor coordination, optic nerve atrophy and enlarged ventricles [44]. These symptoms are all typical of XP [9]. Thus neurological disease in this patient is likely due to defective NER, rather than the loss of another function of ERCC1-XPF. Thus it appears that *Ercc1*^{-/-} and *Xpf*^{-/-} mice are currently the best model of XP neurological disease. Unfortunately, there is early onset and rapid progression of symptoms in these short-lived strains, which is not the case in many XP patients. Greater promise perhaps lies in using conditional knock-out strains [51] or strains with reduced expression of ERCC1-XPF ([52] and Niedernhofer unpublished data).

TC-NER

Csa and Csb—Deletion of *Csb* in mice causes a phenotype significantly milder than CS [53]. Male mice display a mild growth defect (12% decrease in body weight) and both genders show very mild neurological disease, including decreased motor activity in an open field test and impaired sensorimotor coordination (decreased latency to fall from a rotarod), indicative of defects in the basal ganglia and cerebellum. Tremors, gait disturbance and ataxia are notably absent. Demyelination of neurons, characteristic of CS, is also absent in the mouse [53]. *Csa*^{-/-} mice do not appear to have any neurologic abnormalities [54]. Also atypical of CS, both *Csb*^{-/-} and *Csa*^{-/-} mice are highly susceptible to UV-induced skin cancer [53,54].

Deleting *Xpa* in *Csb*^{-/-} mice (*Csb*^{-/-};*Xpa*^{-/-}) causes profound growth retardation, neurologic symptoms and a severe reduction in lifespan (maximum 3 wks) [55,56]. Neurologic symptoms include tremors, an abnormal gait, dystonia, poor balance and progressive ataxia in the first week of life [55,56]. Neuropathological findings in the cerebellum include decreased foliation, decreased neuronal proliferation and increased apoptosis in the external granular layer, as well as decreased arborization of Purkinje cell dendrites [55]. Not surprisingly, *Csb*^{-/-};*Xpc*^{-/-} mice, defective in both TC-NER and GG-NER have what appears to be a phenotype identical to *Csb*^{-/-};*Xpa*^{-/-} mice [57]. Thus deletion of NER in these TC-NER mutants has a synergistic effect on disease, presumably because spontaneous DNA damage accumulates much more rapidly. What is not known is if neurological disease in these double mutant strains is more similar to XP or CS. This awaits further analysis to determine if the primary defect is neurodegeneration (XP) or demyelination (CS).

Xpd—To create a mouse model of TTD, the murine *Xpd* locus was targeted with a construct containing 194 basepairs from the 3' end of human *XPD* cDNA with a disease-causing point mutation (R722W), and homozygous mutant mice bred [12]. *Xpd*^{TTD/TTD} mice mimic many aspects of TTD including brittle hair, skin abnormalities (ichthyosis, acanthosis and hyperkeratosis), cachexia, growth retardation, UV sensitivity and reduced lifespan, although the phenotype is milder than the human disease. A hallmark feature of TTD, including patients with the R722W mutation, is impaired intelligence. However, the only apparent neurological abnormality in *Xpd*^{TTD/TTD} mice is tremors. Myelination in the PNS appeared normal [12]. The relative weight of the brain of *Xpd*^{TTD/TTD} mice is maintained throughout their lifespan, indicating that the mice do not suffer from cerebral atrophy [58].

Very recently Jean-Marc Egly's group examined the neuropathology in *Xpd*^{TTD/TTD} more thoroughly [59]. Three week old mice showed microcephaly and demyelination in the striatum, corpus callosum and thalamus. These defects correlate with decreased transcription of genes regulated by thyroid hormone, a key mediator of neuron migration, growth of neuronal processes, myelination and synaptogenesis in brain development [59]. This study reveals a novel function of TFIIH: stabilizing thyroid hormone receptors on their responsive elements in promoters of genes expressed in the CNS. These data suggest that much of the neuropathology seen in TTD and CS may not be due to faulty DNA repair and accumulated spontaneous DNA damage, but to defective transcription.

Similar to *Csb*, breeding *Xpd*^{TTD/TTD} mice into an XPA-deficient background, to disrupt all NER, exacerbates the phenotype [60]. *Xpd*^{TTD/TTD};*Xpa*^{-/-} mice spontaneously develop osteoporosis leading to kyphosis and accelerated aging of the epidermis. In addition, their gait is abnormal, indicating increased neurological dysfunction [60]. This suggests that transcription is further compromised in these mice as a consequence of unrepaired DNA damage. Genes required to maintain neurological function could be directly damaged. Or stochastic damage could further compromise TFIIH levels, potentially by stabilizing the transcription factor at or near sites of damage.

To create a mouse model of XP-CS (a rare syndrome with symptoms associated with both XP and CS), a disease-causing point mutation (G602D) was knocked into the murine *Xpd* locus [61]. Similar to the human syndrome, *Xpd*^{CS/CS} mice are hypersensitive to UV and have delayed development and a propensity for skin cancer. Unlike patients, neurologic symptoms are mild and not progressive. They include dystonia and spasticity in pre-pubescent male mice only. Notably, the mice have normal sensorimotor coordination and are not ataxic. However, *Xpd*^{CS/CS};*Xpa*^{-/-} mice develop progressive ataxia, spasticity and gait abnormalities beginning in the first week of life. Histopathologic examination revealed degeneration of Purkinje cells but not other neurons in the cerebellum or cerebrum [61].

Xpg—XPG is the endonuclease that makes the incision 3' of the lesion in NER [62]. It is also required to stabilize TFIIH [4]. Deletion of *Xpg* in the mouse leads to post-natal growth retardation and death before weaning [63]. In addition, the mice display progressive neuropathological disease including tremors, reduced spontaneous activity, ataxia and poor balance [64]. Purkinje cells in the cerebellum of *Xpg*^{-/-} mice are atrophic with decreased dendritic arborization, with apoptosis of neurons in the external granular layer. These symptoms and histopathologic findings are similar to mice with cerebellar atrophy and Purkinje cell degeneration [65], suggesting that neurons in the cerebellum are particularly sensitive to spontaneous DNA damage. Granule cells release neurotrophins which are important for cerebellar development and Purkinje cell dendritogenesis [66,67]. Therefore apoptosis of granule cells could alternatively be the primary defect leading to Purkinje cell atrophy and loss of coordinated movement.

Xpg^{E791A/E791A} and *Xpg*^{D811A/D811A} mice homozygous for point mutations in two amino acid residues essential for the nuclease activity of XPG develop normally [68,69]. However, the mice and cells derived from them are hypersensitive to UV. Thus deleting the nuclease activity of XPG in the mouse mimics deletion of *Xpc* or *Xpa*, indicating that neurodegeneration in *Xpg*^{-/-} mice cannot be attributed to a defect in TC-NER, which requires both XPA and XPG nuclease activity. Neurodegeneration, therefore most likely is a consequence of impaired transcription.

Truncation of XPG in exon 11 (of 15), leading to deletion of the highly conserved C-terminus, causes a phenotype similar to, but slightly milder than, deletion of the entire gene [69]. Deletion of exon 15 only, which is not conserved, has no effect on mice [69]. However, combining this mutation with deletion of *Xpa* leads to a phenotype like *Xpg*^{-/-} mice [70]. As discussed above, *Csb*^{-/-} mice have a mild phenotype. But *Csb*^{-/-};*Xpa*^{-/-} mice have profound growth retardation and progressive neurodegeneration [55]. *Xpg*^{-/-} and *Csb*^{-/-};*Xpa*^{-/-} mice are phenotypically identical. This suggests that XPG and CSB facilitate transcription in a like manner. One plausible interpretation of these complex phenotypes is that in the absence of XPG or CSB, transcription of a damaged genome leads to a cytotoxic intermediate. The neurodegeneration in *Xpg*^{-/-} and *Csb*^{-/-};*Xpa*^{-/-} mice may be caused by high levels of transcription in neurons or spontaneous DNA damage in neurons.

Xab2—XAB2 (XPA-binding protein 2) interacts with XPA, CSA, CSB and RNA polymerase II. The exact function of XAB2 in TC-NER is not known. However, immunodepletion of XAB2 or siRNA knock-down causes UV hypersensitivity, impairs RNA synthesis following UV irradiation of cells, as well as inhibiting transcription [71,72]. In the mouse, deletion of *Xab2* or even just the C-terminal 162 amino acids of the protein (removing the 15th tetratricopeptide motif involved in protein:protein interactions) causes early embryonic lethality (E3.5) [73]. This cannot be attributed to defective TC-NER, but must be due to other functions of XAB2 in the cell. Recently, the human protein was co-purified as part of a large protein complex involved in pre-mRNA splicing [72], similar to orthologs in lower eukaryotes.

XAB2 may prove to be required for neurogenesis and brain development. Deletion of *crn*, a *Drosophila* homolog, impairs proliferation of brain neuroblasts and development of differentiated neuronal lineages in the central and peripheral nervous systems, resulting in lethality at the larval stage [74]. A rat ortholog of human XAB2 and *Drosophila crn* (*Ath55*) is highly expressed in the ventricular zone of the neocortex of developing embryos and neural stem cells, but not in differentiated neurons [75]. Further study with a conditional *Xab2* knock-out will be informative.

Summary

Defects in nucleotide excision repair cause progressive neurological disease. Symptoms in CS and TTD (caused by defects in transcription and TC-NER) overlap considerably with those of XP (caused by defective GG-NER or core NER factors) including dementia, ataxia, spasticity, hearing and visual impairment, peripheral neuropathy, microcephaly and cerebral cortical atrophy. Loss of motor control is more pronounced in XP. Despite the overlap of symptoms, pathogenesis differs. In XP, the primary defect is loss of neurons, suggesting that NER is essential for maintaining neuron function and viability. In CS, demyelination is prominent, suggesting that Schwann cells and oligodendrocytes are more dependent on proteins required for TC-NER.

For the majority of mutant mouse strains generated to model NER-deficiency syndromes, there is a poor correlation between mice and patients with respect to neurological disease. ERCC1-XPF deficient mice appear to be the best model of XP neurodegeneration. *Xpg*^{-/-}, *Csb*^{-/-}; *Xpa*^{-/-}, *Csb*^{-/-}; *Xpc*^{-/-}, *Xpd*^{CS/CS}; *Xpa*^{-/-} mice have similar if not identical phenotypes and appear to be the best model of neurological disease in CS or TTD. But for both diseases, further work is required to determine if the mechanism of pathogenesis in mice is similar to humans.

In general, mouse models of NER deficiency have a milder phenotype than the human diseases they model. This in fact holds true for many genome instability disorders (*e.g.*, Werner syndrome, Bloom's syndrome and Fanconi anemia). It is possible that mice have decreased spontaneous DNA damage relative to humans or have greater tolerance for unrepaired damage. However, this seems unlikely based on the observation that deletion of *Xpa* exacerbates the phenotype of all mouse models of CS and TTD dramatically. Another possible explanation is that environmental exposures strongly influence the level of spontaneous DNA damage. Experimental mice are kept under a highly controlled conditions that don't mimic of the complex environment in which humans live. Thus although neurological disease in NER-deficiency has been traditionally thought of as being driven by endogenous DNA damage, the fact that NER-deficient mice have significantly less neuropathology than humans, may mean that the damage is strongly influenced by environmental factors and therefore could be avoided to delay disease.

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Figure 1. Schematic diagram of nucleotide excision repair highlighting mutant mouse strains available

Two subpathways of NER are delineated based on the location of a DNA lesion in the genome and how the damage is recognized. XPC-HR23B binds helix-distorting lesions throughout the genome in global genome-NER (GG-NER). This is facilitated by the DDB complex (DDB1 and XPE/DDB2) specifically in the case of damage caused by UV-irradiation. DDB is part of the Cul4A complex, which ubiquitylates XPC leading to stable association of this protein to damaged DNA. Lesions on the transcribed strand of genes can block RNA polymerase II-mediated transcription, leading to activation of transcription-coupled NER (TC-NER). Either XPC in GG-NER or CSA and CSB in TC-NER recruit the multi-subunit transcription factor TFIID (subunits indicated with dots). XPG is required to stabilize TFIID. The XPB and XPD subunits of TFIID are helicases that unwind the DNA around the lesion. XPA and RPA then bind and stabilize the open structure and recruit ERCC1-XPF. This nuclease incises the damaged strand of DNA 5' to the lesion. XPG makes the 3' incision. The lesion is removed in a single-stranded oligonucleotide, leaving behind a gap that is filled by the replication machinery (polymerase δ and ϵ , PCNA, RPA and RFC). The DNA backbone is sealed by DNA ligase I.

Colored circles indicate gene products that have been targeted in the mouse. -/- indicates mutant strains where the protein of interest is undetectable. Homozygous deletion of *Ddb1*, *Xab2*, *Xpb* or *Xpd* is incompatible with life. Thus *Ddb1* was conditionally knocked out (F/F = floxed

allele) and point mutations in *Xpd* causing TTD or CS were knocked into the mouse genome (m/m).

Table I

Comparison of neurological disease in patients with inherited defects in nucleotide excision repair and mouse models of their diseases. Shading indicates gene products that have functions distinct from NER. XP neurodegeneration includes progressive loss of fine motor control, dementia, choreoathetosis, ataxia, unsteady gait, spasticity, rigidity, hyporeflexia, loss of hearing, laryngeal dystonia and dysarthria, dysphagia and peripheral sensory axonal neuropathy [9,13]. CS neurological disease begins post-natally and can progress rapidly (years) or slowly (decades). Symptoms includes microcephaly, mental retardation, dementia, spasticity, tremor, ataxia, gait abnormalities, hypo- or hyper-reflexia, progressive hearing loss and visual impairment [10,11].

Gene		Function in NER	Neurological disease in humans	Neurological disease in mice
GG-NER	<i>Xpc</i>	Recognition of DNA damage	Adult-onset XP neurodegeneration [17].	None reported [24,25].
	<i>Hr23a</i>	Stabilize XPC	<i>No patients</i>	None reported [30].
	<i>Hr23b</i>	Stabilize XPC	<i>No patients</i>	Deletion of <i>mHR23B</i> causes embryonic lethality (E15.5). Behavioral abnormalities occur in the fraction of mice that live [29].
	<i>Xpe/Ddb2</i>	Stabilize XPC after UV damage	None reported [19].	None reported [39,40].
	<i>Ddb1</i>	Stabilize XPC after UV damage	<i>No patients</i>	Deletion of <i>Ddb1</i> causes embryonic lethality (E12.5); Deletion of <i>Ddb1</i> in the brain causes apoptosis of neuronal progenitors leading to abnormal brain development [38].
TC-NER	<i>Csa</i>	Recruits TFIIH	CS neurological disease [11].	None reported [54].
	<i>Csb</i>	Recruits TFIIH to promoters of damaged genes where RNA pol II is stalled	CS neurological disease [11].	Mild defects in sensorimotor coordination and motor activity [53]. Simultaneous deletion of <i>Xpa</i> or <i>Xpc</i> leads to postnatal tremors, abnormal gait, dystonia, poor balance and progressive ataxia due to cerebellar hypoplasia [55, 57].
	<i>Xab2</i>	Binds CSA, CSB, RNA pol II & XPA	<i>No patients</i>	Deletion of <i>Xab2</i> causes early embryonic lethality (E3.5) [73].
	<i>Xpd</i>	Subunit of TFIIH; helicase	Juvenile to onset of XP neurodegeneration or CS neurological disease [76].	A point mutation linked to TTD causes tremors, microcephaly and patchy demyelination [12,59]. Simultaneous deletion of <i>Xpa</i> leads to gait abnormalities [60]. A point mutation linked with XP-CS causes transient dystonia and spasticity in juvenile male mice [61]. Simultaneous deletion of <i>Xpa</i> causes progressive postnatal ataxia, spasticity and gait abnormalities [61].
	<i>Xpg</i>	3' nuclease in NER; binds and stabilizes TFIIH	Juvenile to adult onset XP neurodegeneration or CS neurological disease [77].	Deletion of <i>Xpg</i> causes progressive ataxia due to atrophy of cerebellar Purkinje cells and apoptosis of granule cells [64].
GG- & TC-NER	<i>Xpa</i>	Stabilizes open intermediate; recruits ERCC1	Juvenile to adult onset of XP neurodegeneration [9].	None reported [41,42].
	<i>Ercc1</i>	Subunit of 5' nuclease	Microcephaly, cerebellar hypoplasia and reduced foliation [48].	Deletion of <i>Ercc1</i> causes progressive dystonia, tremors and ataxia [44,50], cerebellar hypoplasia and reduced foliation [48].
	<i>Xpf</i>	Catalytic subunit of 5' nuclease	Juvenile to adult onset of XP neurological disease [18,44].	Deletion of <i>Xpf</i> causes a phenotype similar to <i>Ercc1</i> ^{-/-} mice [49].