Title:

Xeroderma Pigmentosum: overview of pharmacology and novel therapeutic strategies for neurological symptoms.

Running Title

Potential therapeutics on XP neurological symptoms

Authors

Rosella Abeti¹, Anna Zeitberger¹, Colm Peelo¹, Hiva Fassihi², Robert P. E. Sarkany², Alan R. Lehmann³ and Paola Giunti¹².

¹ Ataxia Centre, Department of Molecular Neuroscience, University College London, Institute of Neurology London, WC1N 3BG, United Kingdom.

² National Xeroderma Pigmentosum Service St John's Institute of Dermatology Guy's and St Thomas' Foundation Trust London SE1 7EH United Kingdom.

³ Genome Damage and Stability Centre, University of Sussex, Falmer, Brighton BN1 9RQ United Kingdom.

Abstract

Xeroderma Pigmentosum (XP) encompasses a group of rare diseases characterised in most cases by nucleotide excision repair (NER) malfunction, resulting in an increased sensitivity to ultraviolet radiation in affected individuals. Approximately 25-30% of XP patients present with neurological symptoms, such as sensorineural deafness, mental deterioration, and ataxia. Although it is known that dysfunctional DNA repair is the primary pathogenesis in XP, growing evidence suggests that mitochondrial pathophysiology may also occur. This appears to be secondary to dysfunctional NER but may contribute to the neurodegenerative process in these patients. The available pharmacological treatments in XP mostly target the dermal manifestations of the disease. In the present review, we outline how current understanding of the pathophysiology of XP could be used to develop novel therapies to counteract the
neurological symptoms. Moreover, the coexistence of cancer and neurodegeneration present in XP, lead us to focus on possible new avenues targeting mitochondrial pathophysiology.

Abstract=149 words

**Abbreviations:** XP, Xeroderma Pigmentosum; UV, Ultraviolet; NER, Nucleotide excision repair; ETC, electron transport chain; $\Delta \Psi_m$, mitochondrial membrane potential; OXPHOS, Oxidative phosphorylation; mtDNA, mitochondrial DNA; ROS, Reactive oxygen species; CS, Cockayne Syndrome; cyPu, 8,5-cyclopurine deoxynucleotides; SSB, DNA single-strand Break; DSB, DNA double strand-break; CoQ$_{10}$, Coenzyme Q$_{10}$; GPx, Glutathione peroxidase; SOD, Superoxide dismutase; SYT-9, synaptotagmin-9; TrkB, Tropomyosin receptor kinase B; BDNF, brain-derived neurotrophic factor; SARA, Scale for the Assessment and Rating of Ataxia.

**List of Ligands**

rapamycin:
http://www.guidetopharmacology.org/GRAC/LigandTextSearchForward?searchWildcard=rapamycin&order=rank&submitWildcard=Do+wildcard+search

Amitriptyline:
http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=200

BDNF:
http://www.guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=4872
**Introduction**

Xeroderma pigmentosum (XP) is an autosomal recessive disorder caused by mutations in genes involved in the DNA repair machinery. XP has an estimated incidence of 2.3 per million live births in Western Europe (Kleijer et al., 2008), but is more common in other geographical regions, including Japan (Hirai et al., 2006). Eight causative proteins have been identified so far (XPA, XPB, XPC, XPD, XPE, XPF, XPG, and XPV), allowing XP to be divided into clinically heterogeneous complementation groups (Bowden et al., 2015; Bootsma & Hoeijmakers, 1991). The XPA to XPG proteins are involved in different steps of the nucleotide excision repair (NER) in the presence of DNA damage. Patients with XP variant (XPV) harbour mutations in the DNA polymerase η, which is involved in DNA synthesis after UV radiation-related damage (Lehmann et al., 1975; Masutani et al., 1999).

The signs and symptoms of patients with XP can broadly be classified into cutaneous and neurological manifestations, although additional symptoms, such as ophthalmological abnormalities and a predisposition to cancers are well recognized (Brooks et al., 2013; Bradford et al., 2011; Fassihi et al., 2016). A recently published study by Fassihi et al. (2016) has provided detailed clinical and molecular information on the largest analyzed cohort of XP patients to date. The study highlighted the clinical heterogeneity of XP even within complementation groups, which is strongly dependent on distinct locations and types of mutations in the causative genes (Fassihi et al., 2016).

**Dermatological symptoms and therapeutic strategies**

XP patients share the common characteristic of extreme sensitivity to ultraviolet (UV) radiation. This may manifest with severe skin burning and blistering in infants, but not all patients exhibit this acute abnormal reaction to sunlight (DiGiovanna & Kraemer, 2012; Sethi et al., 2013; Fassihi et al., 2016). Freckling-like skin changes, however, develop in all patients and eventually progress into atrophy, telangiectasias and intermixed hypo- and hyperpigmented areas (Black, 2016). Premalignant lesions, such as actinic keratoses and skin neoplasms in sun-exposed areas, are observed at an early age, and are related to complementation group (DiGiovanna & Kraemer, 2012). The most prevalent skin tumors in XP patients are basal and squamous cell carcinomas, followed by malignant melanomas, with a 10,000-fold and 2,000-fold increased incidence respectively (Bradford et al., 2011). Interestingly, complementation groups presenting with an abnormal acute sunburn reaction...
are associated with neurodegeneration, but also with a lower prevalence of skin cancer due to early diagnosis and initiation of sun protection (Sethi et al., 2013; Fassihi et al., 2016).

In the absence of specific treatments that target the underlying DNA-repair dysfunction, the multidisciplinary clinical management of XP patients mainly focuses on strict UV-protection and treatment of malignancies (Tamura et al., 2014). The former encompasses the reduction of exposure to sunlight using UV-protective long-sleeved clothing, filters on windows in buildings and cars, and sunscreen lotions with the highest possible protective filters (Moriwaki et al., 2017). Regular skin cancer screening is essential to detect early malignancies, which are treated in accordance with guidelines used for non-XP patients (Naik et al., 2013). First-line treatment is surgical excision, but case reports on conservative approaches with topical application of imiquimod 5% (Yang et al., 2015; Malhotra et al., 2008) and 5-fluoruracil (Lambert & Lambert, 2015) have demonstrated favourable results. One prospective randomised-controlled trial suggested a reduced frequency of actinic keratoses and basal cell carcinomas using a liposome preparation containing the bacterial DNA repair enzyme T4N5 endonuclease (Yarosh et al., 2001). However, subsequent studies were terminated due to lack of efficacy (Bulbake et al., 2017).

**Neurological symptoms and lack of causative treatment**

The prevalence of neurodegeneration varies across and even within the complementation groups and is most commonly associated with XPA and XPD, followed by XPB, XPG and XPF (Niedernhofer et al., 2011; Karass et al., 2015; Anttinen et al., 2008; Fassihi et al., 2016). Overall, in Europe and North America approximately 25-30% of XP patients are affected by neurological impairment of variable severity. In affected patients, the progressive cerebral and cerebellar degeneration with frequent involvement of the peripheral nervous system results in a wide range of symptoms including (I) progressive cognitive impairment, (II) sensorineural hearing loss, (III) ataxia, (IV) pyramidal, and (V) extrapyramidal tract signs, and (VI) areflexia (Rass et al., 2007; Niedernhofer, 2008; Lehmann et al., 2011; Fassihi et al., 2016). The mean age of death of affected patients has been reported as 29 years, compared to 37 years in patients without neurodegeneration (Bradford et al., 2011).

To date, there is no effective treatment for the neurological manifestations of XP, and symptoms are managed with supportive measures. Exposure to UV-B radiation is crucial in cutaneous carcinogenesis in XP, however the aetiology of the neurological symptoms is poorly understood. Recently, it has been found that NER is required not only for repair of
ultraviolet radiation damage but also of some endogenous DNA lesions due to generation of reactive species (reviewed by Brooks et al., 2017). These lesions are generated by the reaction of hydroxyl radicals with DNA, forming 8,5-cyclopurine deoxynucleotides (cyPu). Tomas Lindahl (Kuraoka et al., 2000), and Jay Robbins (Brooks et al., 2000) groups reported that cyPu are exclusive substrates for NER, suggesting that mutations in this specific DNA repair process contribute to the neurological symptoms in XP (reviewed by Brooks et al., 2017). An improved understanding of the pathophysiology of neurological dysfunction, which will be discussed later in the review, seems crucial for the development of causative treatment.

Related disorders
The most closely related NER disorder to XP is Cockayne Syndrome (CS). CS-A is caused by mutations of the ERCC8 gene, while CS-B patients harbour mutations in the ERCC6 gene (Spivak, 2004). The CS-A and CS-B proteins are required for a sub-branch of NER (transcription-coupled-NER) that rapidly repairs damage in the transcribed strand of actively transcribed genes (Kamenisch et al., 2010). They also have a role in transcription and neuronal differentiation (Wang et al., 2014). CS has a severe developmental and neurological phenotype, which overlaps with the relatively milder neurological phenotype of XP (Kraemer et al., 2007). Neurological manifestations include progressive spasticity, peripheral neuropathy, ataxia, weakness and dementia. Underlying these impairments is both a failure of brain development and progressive neuronal loss. Although patients are photosensitive, CS is not associated with an increased risk of skin malignancies (Rapin et al., 2006). Life expectancy is markedly reduced in all patients, but differs according to clinical subtype (Rapin et al., 2006). XP-CS complex refers to a rare neurodegenerative disorder that combines clinical characteristics of XP and CS. Patients present with growth retardation and neurodevelopmental decline, while at the same time suffering from the cutaneous manifestations observed in XP (Natale & Raquer, 2017). Although CS and XP have different genetic defects, they share cellular hypersensitivity to UV radiation and defective NER, which will be further discussed below.

Other related disorders that share some clinical and molecular features with XP include: (I) ataxia telangiectasia (AT) characterised by a similar neurological phenotype and the occurrence of cancer; (II) ataxia with oculomotor apraxia type 1 (III) and 2 (AOA1; AOA2; Clements et al., 2004), (IV) spinocerebellar ataxia with axonal neuropathy (SCAN1; El-Khamisy et al., 2005; Gilmore, 2014), (V) and Riddle syndrome (Stewart et al., 2009), sharing some neurological feature such as ataxia and with underlying DNA repair defects.
Mitochondrial dysfunction is a common pathophysiological feature of all these disorders (Le, I et al., 2007; Scheibye-Knudsen et al., 2013), and although the cause of cancer in XP is molecularly understood the pathophysiology causing neurodegeneration is an emerging matter of debate (Table 1).

**Pathophysiology**

**Oxidative Damage in XP**

Oxidative stress and cumulative oxidative DNA damage in neurons are the primary causes of neurodegeneration (Hayashi, 2009; Niedernhofer et al., 2011). Neurons have a high metabolic load and are thus sensitive to alterations in energy metabolism (Rothe et al., 1993). High oxygen consumption leads to greater generation of reactive oxygen species (ROS) (Hayashi, 2009). Endogenous genotoxic processes, such as defective oxidative cellular metabolism and ROS generation, can alter cell integrity as well as result in many different types of oxidative DNA damage. Most of this damage, such as single strand breaks and oxidized purines and pyrimidines, is repaired by processes such as base excision repair that are not deficient in XP. However, as described above, certain types of oxidative damage such as cyclopurines can only be repaired by NER and so are thought to accumulate in XP (Brooks et al., 2000; Kraemer et al., 2007; Brooks, 2008). This unrepaird oxidative DNA damage accumulates over time in terminally differentiated post-mitotic cells such as neurons and has deleterious effects on transcription and apoptosis regulation, resulting in neurodegeneration.

Silencing the genes that produce the NER proteins, CSA, CSB, XPA, and XPC, alters redox homeostasis by increasing ROS levels, affecting oxidative phosphorylation (OXPHOS) and cell energy metabolism through oxidative damage to electron transport chain (ETC) subunits and membrane phospholipids (Brennan-Minnella et al., 2016; Parlanti et al., 2015). This leads to a further increase in oxidative stress (Kowaltowski & Vercesi, 1999). XPC-downregulation also resulted in an increase in oxidative nuclear and mitochondrial DNA damage, impairing OXPHOS (Pascucci et al., 2011). However, mitochondrial DNA (mtDNA) lacks NER, and damage is corrected primarily by base excision repair (Boesch et al., 2011; Wilson, III & Bohr, 2007).
The absence of NER proteins from mitochondria suggests that mitochondrial abnormalities are secondary to nuclear disruptions and the resultant defective signalling pathways (Fang et al., 2014). In addition, the clinical heterogeneity of XP indicates that there are pathological processes occurring beyond the inefficient repair of helix-distorting DNA lesions. Therefore, non-DNA repair related oxidative stress could be involved in the pathogenesis of cancer and neurodegeneration in XP. It may be involved in many different facets causing, and being caused by, many interconnected pathogenic processes, the direction of which is difficult to determine.

**Mitochondrial dysfunction in XP**

Mitochondrial pathophysiology is strictly linked to oxidative stress, as free radicals are normally produced during respiration. Energy production is driven by the activity of the ETC within the mitochondria. ETC generates a proton gradient across the mitochondrial membranes, which is called mitochondrial membrane potential ($\Delta \Psi_m$). The maintenance of $\Delta \Psi_m$ is necessary for functional ETC complexes and normal OXPHOS (Droge, 2002). Changes in $\Delta \Psi_m$, such as hyperpolarisation or depolarisation, are considered pathological because they underlie defects within the ETC. The health of mitochondria is, in fact, pivotal to cellular physiology and, in particular, OXPHOS is critical for cell survival and fundamental for aerobic cell life (Chretien & Rustin, 2003).

The role of mitochondria and oxidative stress in ageing, neurodegeneration and cancer is well established (Plun-Favreau et al., 2010; DiMauro & Schon, 2003). ROS are generated in normal cell metabolism with important roles in cell-signalling for metabolism and growth (Jezeck & Hlavata, 2005; Valko et al., 2007), and are therefore tightly regulated. Increased ROS levels are associated with altered energy states in the ETC (Jezeck & Hlavata, 2005). ETC dysfunction allows more electron leakage and increases ROS production, which is detrimental to the cell (Koopman et al., 2010). ROS can also induce apoptosis directly via death-receptor activation and caspases-8 and -3 (Kulms et al., 2002), but ROS-induced oxidative stress is likely the most significant contributor to cell death (Chretien & Rustin, 2003). Moreover, when ROS generation is not efficiently counteracted by the endogenous antioxidant systems, it increases and subsequently leads to deleterious effects on DNA, lipids and proteins (Cooke et al., 2003; Hayashi, 2009).
Antioxidants [(e.g.: glutathione, coenzyme Q\textsubscript{10} (CoQ\textsubscript{10})) and detoxification enzymes [e.g.: catalase, glutathione peroxidase (GPx), superoxide dismutase (SOD)]] neutralise ROS and represent the primary protection against oxidative stress (Barrientos et al., 2009).

Mechanisms of mitochondrial dysfunction in XP are still a matter for debate. High and prolonged levels of ROS generation have been reported in XP-A, XP-D (Arbault et al., 2004; Arczewska et al., 2013; Parlanti et al., 2015) and XP-C patient cells (Frechet et al., 2008). Additionally, XP-patient cells show remarkably low levels of antioxidants (Nishigori et al., 1989; Vuillaume et al., 1992).

**Mitochondrial dysfunction in CSB**

Although the mitochondrial defect has likewise been considered secondary in CS models, it has been demonstrated that CSB localises to the mitochondria, suggesting a potential role of this protein in mtDNA repair (Arnold et al., 2012). CSB deficient cells showed an increased mitochondrial content, increasing the mitochondrial membrane potential and free radicals, and increased oxygen consumption (Osenbroc et al., 2009; Cleaver et al., 2014). However, these changes did not seem to be related to an increased mitochondrial biogenesis as the transcription factors PGC-1 alpha, TFAM and ERR alpha (the mitochondrial transcription factors related to mitochondrial biogenesis) were not altered in CS-B deficient cells. Since the amount of mitochondria is dependent on biogenesis and degradation, Scheibye-Knudsen et al investigated a probable inhibition of autophagy (Scheibye-Knudsen et al., 2012). Interestingly, they found a decreased co-localization of LC3, P62 and ubiquitin in response to stress in CSB deficient cells, resulting in autophagy inhibition thereby explaining the mitochondrial phenotype. The authors were also able to reverse the phenotype by treating these cells with rapamycin, stimulating autophagy (this will be discussed further below in the text). Moreover, rapamycin seems to be neuroprotective and could potentially attenuate the neurological symptoms in this disease (Bove et al., 2011; Dello et al., 2013). This goes in line with the finding that XPA deficient cells harbour impaired autophagy, leading to increased mitochondrial content, which could contribute to the neurodegenerative phenotype observed in these patients (Fang et al., 2014).

**Potential pharmacological approaches**
Antioxidant therapy with CoQ$_{10}$

The available pharmacological therapy for neurological symptoms in XP patients is limited to symptomatic treatment. As it has been demonstrated that oxidative stress increases and mitochondrial efficiency decreases with age (Bohr et al., 1998; Muller et al., 2007), CoQ$_{10}$ was investigated as a potential therapeutic option. However, these changes cannot be explained by alterations in CoQ$_{10}$ levels as these appear to be stable over time in both control and disease populations (Duncan & Heales, 2005). Preliminary data from our XP cohort of patients (XPA, XPD, XPF and XPG) with variable neurological phenotype showed a trend towards a decreased level of CoQ$_{10}$ concentrations with age in mononuclear cells (MNCs) from XP patients (Giunti personal communication), although the lower levels were still within the normal range. This may suggest a possible decline along with age though not with the severity of the phenotype. This differs with data from Tanaka et al. (1998), reporting a pathological low CoQ$_{10}$ level in plasma that correlated with disease progression (Tanaka et al., 1998). However, the neurological phenotype, in Tanaka et al., was severe and the age of the patients was within a range of 3 to 25 years which appears notably younger than in our cohort (mean: 34 years, range 5 – 46 years). For all this, we can explain the difference in the results achieved by the two studies. Additionally, the CoQ$_{10}$ levels were measured in MNCs and plasma using two different assays.

Interestingly, a decline of CoQ$_{10}$ with age was not observed in XP plasma samples of all complementation groups. However, by measuring the CoQ10 concentration in fibroblasts from two different complementation groups: XPC (prone to cancer) and XPD (severe neuropathology), we found that levels in XPC fibroblasts were similar to controls, while XPD fibroblasts had a significantly lower concentration. This raises the possibility that CoQ$_{10}$ supplementation may be beneficial in XP complementation groups prone to neurodegeneration. Although treatment of CoQ$_{10}$ deficiency and ETC disorders with CoQ$_{10}$ supplementation is difficult owing to the insolubility of CoQ$_{10}$ (Hargreaves, 2014), the above mentioned non-randomised study suggested that an oral dose of 0.9 – 1.5 mg/kg daily improves daily activity in a subset of XP patients (Tanaka et al., 1998). As information about complementation groups was not provided by Tanaka et al., it is not clear whether this subgroup consisted primarily of patients with neurological involvement.

A trial of CoQ$_{10}$ (180 mg per day) in one XPF patient from our cohort was initiated due to constant fatigue, but did not have a beneficial effect on this symptom or the Scale for the Assessment and Rating of Ataxia (SARA) rating scale over the course of 3 years (Giunti
personal communication). Randomised-controlled clinical trials are needed to evaluate the efficacy of CoQ₁₀ supplementation in XP.

**Autophagy stimulation therapy with rapamycin**

An emerging therapy to counteract neurodegeneration is the upregulation of autophagy. This is a physiological process responsible for the removal of misfolded protein aggregates and cellular organelles helping to maintain cellular homeostasis and integrity (Mizushima & Komatsu, 2011). Autophagy is a dynamic recycling system that seems to be downregulated in neurodegeneration in general and in particular in CS and XPA (Scheibye-Knudsen et al., 2012; Fang et al., 2014). Rapamycin is a compound used to activate autophagy through the selective inhibition of the mammalian target of rapamycin (mTOR) and although this can inactivate cell proliferation and survival, it does not affect neurons, as rapamycin showed to be beneficial in neurodegeneration. For example, in Alzheimer’s disease (AD), the most common neurodegenerative disorder, the stimulation of autophagy through rapamycin was associated with upregulation of synapsin I, synapthopsin and post synaptic protein 95 (Anttinen et al., 2008; Singh et al., 2017). These proteins are downregulated in AD and crucial for the maintenance of synaptic integrity. Moreover, oxidative stress, a marker for AD, was also attenuated. Above all, rapamycin is currently in Phase II clinical trials for analogous but different neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (ALS) and Huntington disease (HD).

**Neurite development therapy with Amitriptyline**

Another possible strategy is the usage of Amitriptyline, a tricyclic antidepressant, which is licenced for the treatment of depression and neuropathic pain. As the neuropathophysiology of CSB is characterised by abnormal neuronal development (unlike XP neurons that undergo normal development but degenerate later in life), Wang et al. attempted to rectify this by using Amitriptyline to promote neurite development in cellular models of CS-B (Wang et al., 2016). Further to this, they demonstrated that by upregulating the usually inhibited cascade involving synaptoagmin-9 (SYT-9), neurite proliferation was restored (Wang et al., 2016). Moreover, Amitriptyline was one of the pharmacological agents that upregulated the Tropomysosin receptor kinase B (TrkB) and increased neurite growth (Wang et al., 2016). One of the key mediators of aberrant neuronal development in CSB is SYT-9, which is downregulated in knock down CS-B neurons impeding the formation of neurites (Wang et al., 2016). The SYT family is a group of proteins which regulates membrane trafficking and
fusion (Dean et al., 2012). In particular SYT-1, -2 and -9 are calcium sensors on synaptic vesicles and play a major role in synaptic vesicles membrane fusion events (Yoshihara & Montana, 2004). By upregulating SYT-9 in CS-B models, neurite proliferation was recovered. This was corroborated by pharmacological experiments using amitriptyline, which effectively upregulates TrkB (Wang et al., 2016). This effect is also mimicked by brain-derived neurotrophic factor (BDNF), which is unstable in cultures and degrades quickly compared to Amitriptyline. However, in addition to the beneficial effect of this compound on neurite growth, Amitriptyline appears to induce mitochondrial fragmentation in neuronal models of Parkinson’s disease (Lee et al., 2015). This effect would need to be carefully weighed against possible benefits, and could possibly be counteracted by the addition of antioxidants in the therapeutic regime.

Conclusions
In conclusion, although no pharmacological therapies for neurological symptoms in XP are yet available, we discussed possible avenues that are being investigated to ameliorate these symptoms. We highlighted the possible role for antioxidant therapy with CoQ10 in attenuating the oxidative stress generated by mitochondrial dysfunction, which occurs secondarily to NER deficiency. Furthermore, we raised the possibility of re-activating the autophagic machinery that is downregulated in CS and XPA, with rapamycin, and finally, to restore synaptic contacts by triggering neurite growth with Amitriptyline (Fig. 1).

Words count: 3,264

Nomenclature of Targets and Ligands: Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander et al., 2017).

Competing Interests' Statement: None.
References


Cleaver JE, Brennan-Minnella AM, Swanson RA, Fong KW, Chen J, Chou KM, *et al.* (2014). Mitochondrial reactive oxygen species are scavenged by Cockayne syndrome B


This article is protected by copyright. All rights reserved.
repair have a defect in DNA synthesis after UV-irradiation. *Proc Natl Acad Sci U S A*, 72, 219-223.


Singh, AK, Kashyap, MP, Tripathi, VK, Singh, S, Garg, G & Rizvi, SI. (2017). Neuroprotection Through Rapamycin-Induced Activation of Autophagy and PI3K/Akt1/mTOR/CREB Signaling Against Amyloid-beta-Induced Oxidative Stress, Synaptic/Neurotransmission Dysfunction, and Neurodegeneration in Adult Rats. Mol Neurobiol, 54, 5815-5828.


### Table 1: XP and related disorders.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Protein Function</th>
<th>Defective pathway</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xeroderma Pigmentosum</td>
<td>XPA</td>
<td>Damage verification</td>
<td>NER</td>
<td>40% of the patients show extreme sensitivity to sunlight and sunburn reaction, while 60% do not show any sunburn reaction.</td>
</tr>
<tr>
<td></td>
<td>XPB/ERCC3</td>
<td>Helicase</td>
<td>NER</td>
<td>20/30% of the patients show neurological abnormalities: neuronal degeneration resulting in deafness, ataxia, areflexia, microcephaly and intellectual deficiency and impaired eye sight. XPC, XPE and XPV do not show signs of neurological abnormalities. (Lehmann et al., 2011; Fassihi et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>XPC</td>
<td>Damage recognition</td>
<td>NER</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XPD/ERCC2</td>
<td>Helicase</td>
<td>NER</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XPE/DDB2</td>
<td>Damage recognition</td>
<td>NER</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XPF/ERCC4</td>
<td>Nuclease</td>
<td>NER</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XPG/ERCC5</td>
<td>Nuclease</td>
<td>NER</td>
<td></td>
</tr>
<tr>
<td></td>
<td>XPV/POLH</td>
<td>Polymerase</td>
<td>Translesion synthesis</td>
<td></td>
</tr>
<tr>
<td>Cockayne Syndrome</td>
<td>CSA/ERCC8</td>
<td>Damage recognition</td>
<td>and TC-NER (transcription-coupled nucleotide excision repair)</td>
<td>Microcephaly, ataxia, failure to thrive and delayed development. Increased sensitivity to sunlight (photosensitivity), and in some cases even a small amount of sun exposure can cause a sunburn or blistering of the skin. Hearing loss, vision loss, severe tooth decay, bone abnormalities, abnormal thermoregulation in hands and feet, and liver dysfunction. (Rapin et al., 2006; Wilson et al., 2016)</td>
</tr>
<tr>
<td></td>
<td>CSB/ERCC6</td>
<td>Ubiquitination</td>
<td>Damage recognition</td>
<td></td>
</tr>
<tr>
<td>Ataxia with oculomotor apraxia type 1</td>
<td>DNA-adenylate hydrolase</td>
<td>SSB (DNA single-strand break)</td>
<td>Ataxia, oculomotor apraxia, and peripheral vision. High amounts of a protein AFP in blood. (Clements et al., 2004)</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------</td>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Ataxia with oculomotor apraxia type 2</td>
<td>DNA-RNA helicase</td>
<td>SSB</td>
<td>Ataxia, oculomotor apraxia, and peripheral vision. High amounts of a protein AFP in blood. (Clements et al., 2004)</td>
<td></td>
</tr>
<tr>
<td>Spinocerebellar ataxia with axonal neuropathy</td>
<td>Tyrosyl phosphodiesterase</td>
<td>SSB involved in SSB repair</td>
<td>Spinocerebellar ataxia with axonal neuropathy. (El-Khamisy et al., 2005)</td>
<td></td>
</tr>
</tbody>
</table>
RIDDLE syndrome

Ubiquitination DSB

Microencephaly, facial dysmorphism, telangeiectasia, pulmonary fibrosis, learning difficulties and ataxia. (Stewart et al., 2009)
Figure 1: Therapeutic targets. DNA damage elicits an oxidative stress reaction with a positive feedback which contributes to an even more extensive damage of the DNA. Oxidative stress generated by mitochondria induces hyperpolarization and defective degradation (CoQ$_{10}$ and Rapamycin could counteract these effects). At the same time in neurons synaptic contacts are lost (Amitriptyline increases synaptic clefts).