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REVIEW ARTICLE

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

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Xeroderma pigmentosum (XP) encompasses a group of rare diseases characterized in most cases by malfunction of nucleotide excision repair (NER), which results in an increased sensitivity to UV 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 led us to focus on possible new avenues targeting mitochondrial pathophysiology.

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Abbreviations

$\Delta\Psi_m$, mitochondrial membrane potential; CoQ_{10}, coenzyme Q_{10}; CS, Cockayne syndrome; cyPu, 8,5-cyclopurine deoxynucleotides; ETC, electron transport chain; mtDNA, mitochondrial DNA; NER, nucleotide excision repair; OXPHOS, oxidative phosphorylation; SYT-9, synaptotagmin-9; TrkB, tropomyosin receptor kinase B; XP, xeroderma pigmentosum

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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 (Bootsma and Hoeijmakers, 1991; Bowden *et al.,* 2015). 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 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 (Bradford *et al.,* 2011; Brooks *et al.,* 2013; Fassihi *et al.,* 2016). A recently published study by Fassihi *et al*. (2016) has provided detailed clinical and molecular information on the largest analysed 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 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 and 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 and Kraemer, 2012). The most prevalent skin tumours in XP patients are basal and squamous cell carcinomas, followed by malignant melanomas, with a 10 000-fold and 2000-fold increased incidence respectively (Bradford *et al.,* 2011). Interestingly, complementation groups presenting with an abnormal acute sunburn reaction are associated not only 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% (Malhotra *et al.,* 2008; Yang *et al.,* 2015) and **5-fluorouracil** (Lambert and Lambert, 2015) have demonstrated favourable results. One prospective randomized 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.

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 (Anttinen *et al.,* 2008; Niedernhofer *et al.,* 2011; Karass *et al.,* 2015; 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 for repair not only of UV radiation damage but also of some endogenous DNA lesions due to generation of reactive species (see Brooks, 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 (see Brooks, 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 and 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 the following: (i) ataxia telangiectasia characterized 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); and (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 Ber *et al.,* 2007; Scheibye-Knudsen *et al.,* 2013), and although the cause of cancer in XP is molecularly understood, the pathophysiology causing neurodegeneration is still a 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 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 unrepaired 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 the electron transport chain (ETC) subunits and membrane phospholipids (Parlanti *et al.,* 2015; Brennan-Minnella *et al.,* 2016). This leads to a further increase in oxidative stress (Kowaltowski and Vercesi, 1999). *XPC* down-regulation also resulted in an increase in oxidative nuclear and mitochondrial DNA (mtDNA) damage, impairing OXPHOS (Pascucci *et al.,* 2011). However, mtDNA lacks NER, and damage is corrected primarily by base excision repair (Wilson and Bohr, 2007; Boesch *et al.,* 2011).

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 aspects, 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, which generates a proton gradient across the mitochondrial membranes, called the 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 hyperpolarization or depolarization, 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 and Rustin, 2003).

The role of mitochondria and oxidative stress in ageing, neurodegeneration and cancer is well established (DiMauro and Schon, 2003; Plun-Favreau *et al.,* 2010). ROS are generated in normal cell metabolism with important roles in cell signalling for metabolism and growth (Jezek and Hlavata, 2005; Valko *et al.,* 2007) and are therefore tightly regulated. Increased ROS levels are associated with altered energy states in the ETC (Jezek and 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 and 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, such as glutathione and coenzyme Q_{10} (CoQ_{10}), and detoxification enzymes, such as catalase,

Table 1

XP and related disorders

Disease	Gene	Protein function	Defective pathway	Clinical features
Xeroderma pigmentosum	XPA XPB/ERCC3 XPC XPD/ERCC2 XPE/DDB2 XPF/ERCC4 XPG/ERCC5 XPV/POLH	Damage verification Helicase Damage recognition Helicase Damage recognition Nuclease Nuclease Polymerase	NER NER NER NER NER NER NER Translesion synthesis	40% of the patients show extreme sensitivity to sunlight and sunburn reaction, while 60% do not show any sunburn reaction. 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)
Cockayne syndrome	CSA/ERCC8 CSB/ERCC6	Damage recognition and Ubiquitination Damage recognition	TC-NER (transcription-coupled NER)	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)
Ataxia telangiectasia	ATM	Damage-activated protein kinase	DSB (DNA double strand-break)	Ataxia, chorea, myoclonus neuropathy. Slurred speech and oculomotor apraxia. Small clusters of enlarged blood vessels called telangiectases, which occur in the eyes and on the surface of the skin, are also characteristic of this condition.High amounts of a protein called α-fetoprotein (AFP) in the blood.
Ataxia with oculomotor apraxia type 1	–	DNA-adenylate hydrolase	SSB (DNA single-strand Break)	Ataxia, oculomotor apraxia and peripheral vision. (Clements *et al.,* 2004)
Ataxia with oculomotor apraxia type 2	–	DNA–RNA helicase	SSB	Ataxia, oculomotor apraxia and peripheral vision. High amounts of a protein AFP in blood. (Clements *et al.,* 2004)
Spinocerebellar ataxia with axonal neuropathy	–	Tyrosyl phosphodieaterase involved in SSB repair	SSB	Spinocerebellar ataxia with axonal neuropathy.El-Khamisy *et al.,* 2005)
RIDDLE syndrome	–	Ubiquitination	DSB	Microencephaly, facial dysmorphism, telangeiectasia, pulmonary fibrosis, learning difficulties and ataxia. (Stewart *et al.,* 2009)

glutathione peroxidase and SOD, neutralize 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 CS-B patients

Although the mitochondrial defect has likewise been considered secondary in CS models, it has been demonstrated that the CS-B protein localizes to the mitochondria, suggesting a potential role of this protein in mtDNA repair (Arnold *et al.,* 2012). CS-B-deficient cells showed an increased mitochondrial content, increasing the $\Delta\Psi_m$ and free radicals, and increased oxygen consumption (Osenbroch *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-1α, TFAM and ERRα (the mitochondrial transcription factors related to mitochondrial biogenesis) were not altered in CS-B-deficient cells. As the amount of mitochondria is dependent on biogenesis and degradation, Scheibye-Knudsen *et al.* (2012) investigated a probable inhibition of autophagy. Interestingly, they found a decreased co-localization of LC3, P62 and http://www.

guidetopharmacology.org/GRAC/LigandDisplayForward?ligandId=4789 in response to stress in CS-B-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 is compatible 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 and 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 pathologically 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 that 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 CoQ_{10} 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-randomized study suggested that an oral dose of 0.9–1.5 $mg \cdot kg^{-1}$ 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 $mg \cdot day^{-1}$) 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 rating scale over the course of 3 years (Giunti, *personal communication*). Randomized controlled clinical trials are needed to evaluate the efficacy of CoQ_{10} supplementation in XP.

Autophagy stimulation therapy with rapamycin

An emerging therapy to counteract neurodegeneration is the up-regulation 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 and Komatsu, 2011). Autophagy is a dynamic recycling system that seems to be down-regulated in neurodegeneration in general and in particular in CS and XPA (Scheibye-Knudsen *et al.,* 2012; Fang *et al.,* 2014). Rapamycin is used to activate autophagy through the selective inhibition of the **mechanistic target of rapamycin kinase (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 up-regulation of synapsin I, synapthopysin and postsynaptic protein 95 (Anttinen *et al.,* 2008; Singh *et al.,* 2017). These proteins are down-regulated in AD and crucial for the maintenance of synaptic integrity. Moreover, oxidative stress, a marker for AD, was also attenuated. Above all, rapamicyin is currently in phase II clinical trials for analogous but different neurodegenerative disorders such as amyotrophic lateral sclerosis and Huntington disease.

Neurite development therapy with amitriptyline

Another possible strategy is the use of **amitriptyline**, a tricyclic antidepressant, which is licenced for the treatment of depression and neuropathic pain. As the neuropathophysiology of CS-B is characterized by abnormal neuronal development (unlike XP neurons that undergo normal development but degenerate later in life), Wang *et al*. (2016) attempted to rectify this by using amitriptyline to promote neurite development in cellular models of CS-B. Further to this, they demonstrated that by up-regulating the usually inhibited cascade involving synaptotagmin-9 (SYT-9), neurite proliferation was restored (Wang *et al.,* 2016). Moreover, amitriptyline was one of the pharmacological agents that up-regulated the **tropomyosin receptor kinase B (TrkB)** and increased neurite growth (Wang *et al.,* 2016). One of the key mediators of aberrant neuronal development in CS-B is SYT-9, which is down-regulated 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

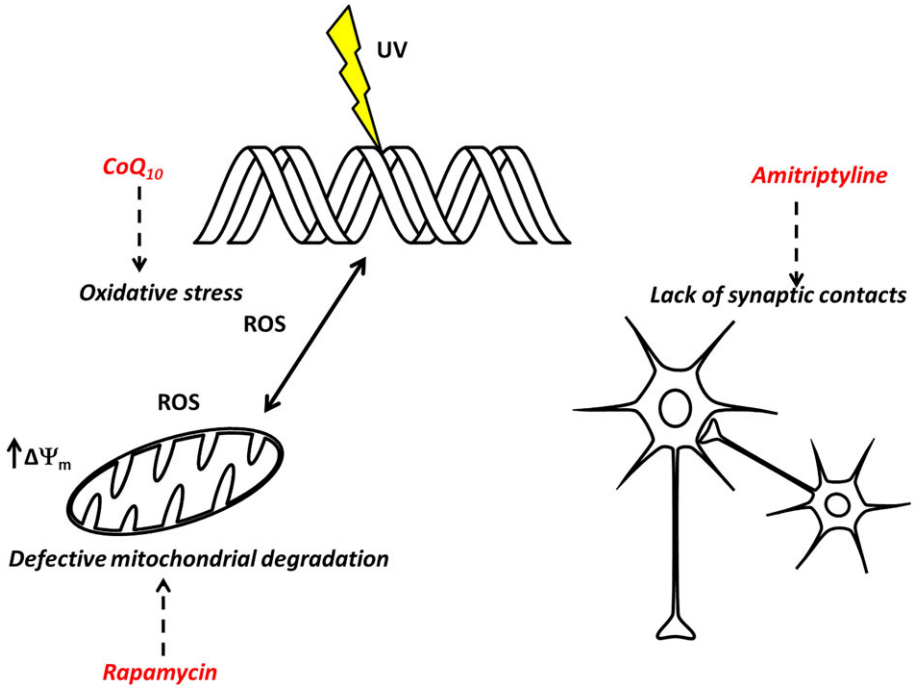

Figure 1
Therapeutic targets. DNA damage elicits an oxidative stress reaction with a positive feedback which contributes to an even more extensive damage of the DNA. Oxidative stress generated by mitochondria induces hyperpolarization and defective degradation (CoQ_{10} and rapamycin could counteract these effects). At the same time in neurons, synaptic contacts are lost (amitriptyline increases synaptic clefts).

synaptic vesicles membrane fusion events (Yoshihara and Montana, 2004). By up-regulating SYT-9 in CS-B models, neurite proliferation was recovered. This was corroborated by pharmacological experiments using amitriptyline, which effectively up-regulates TrkB (Wang *et al.,* 2016). This effect is also mimicked by **brain-derived neurotrophic factor**, 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 have, here, discussed possible avenues that are being investigated to ameliorate these symptoms. We highlighted the possible role for antioxidant therapy with CoQ_{10} 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 down-regulated in CS and XPA, with rapamycin, and finally, to restore synaptic contacts by triggering neurite growth with amitriptyline (Figure 1).

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).

Conflict of interest

The authors declare no conflicts of interest.

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