Title:

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

Running Title

Potential therapeutics on XP neurological symptoms

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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

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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, synamtotagmin-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 a*l., 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 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 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 (Jezek & Hlavata, 2005; Valko *et al.*, 2007), and are therefore tightly regulated. Increased ROS levels are associated with altered energy states in the ETC (Jezek & 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_{10} (CoQ_{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 suggests 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 CoQ_{10} 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, synapthopysin 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, rapamicyin 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 synaptotagmin-9 (SYT-9), neurite proliferation was restored (Wang *et al.*, 2016). Moreover, Amitriptyline was one of the pharmacological agents that upregulated the Tropomyosin 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 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 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.

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***Table 1*: XP and related disorders.**

Disease	Gene	Protein Function	Defective pathway	Clinical Features
Xeroderma Pigmentosum	XPA	Damage verification	NER	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)
	XPB/ERCC3	Helicase	NER	
	XPC	Damage recognition	NER	
	XPD/ERCC2	Helicase	NER	
	XPE/DDB2	Damage recognition	NER	
	XPF/ERCC4	Nuclease	NER	
	XPG/ERCC5	Nuclease	NER	
	XPV/POLH	Polymerase	Translesion synthesis	
Cockayne Syndrome	CSA/ERCC8	Damage recognition and Ubiquitination	TC-NER (transcription-coupled nucleotide excision repair)	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)
	CSB/ERCC6	Damage recognition		

Ataxia Talangectasia	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 alpha-fetoprotein (AFP) in blood. (Gilmore, 2009)
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)

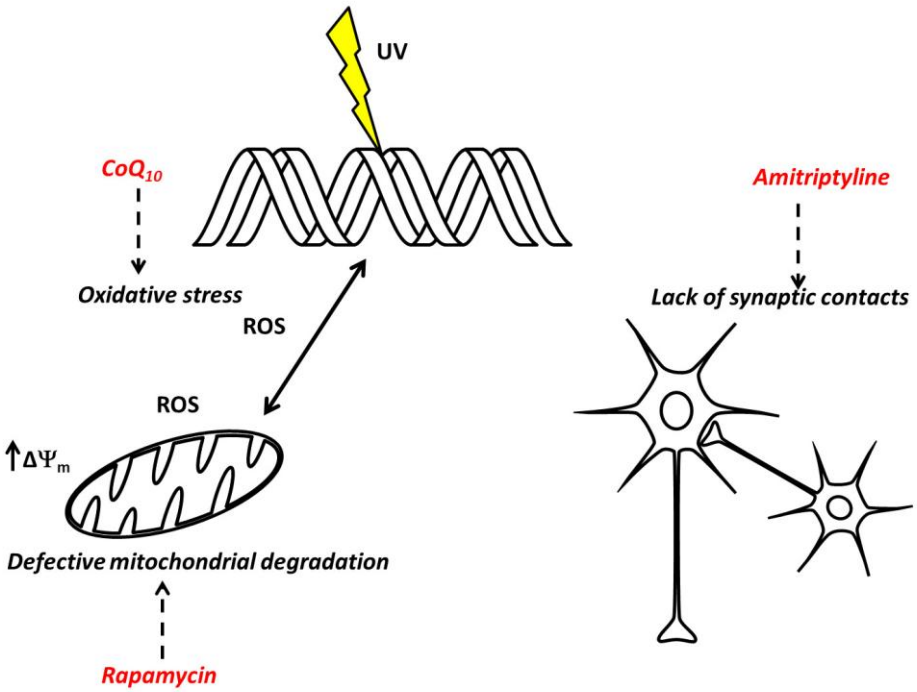

***Figure 1*: Therapeutic targets**. DNA damage elicits an oxidative stress reaction with a positive feedback which contributes to an even more extensive damage of the DNA. Oxidative stress generated by mitochondria induces hyperpolarization and defective degradation (CoQ_{10} and Rapamycin could counteract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