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Overview Of Pharmacology And New Treatment Approaches For Neurological Disorders Associated With Xeroderma Pigmentosum

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Abstract :
The term "xeroderma pigmentosum" (XP) refers to a collection of uncommon disorders that are primarily defined by nucleotide excision repair (NER) dysfunction, increasing the susceptibility of those afflicted to UV light. A small percentage of XP patients—between 25 and 30 percent—have neurological symptoms such ataxia, mental decline, and sensorineural deafness. While the primary etiology of XP is known to be faulty DNA repair, there is mounting evidence that mitochondrial pathology may also be present. Although it seems to be a result of malfunctioning NER, this could accelerate the neurodegenerative process in these individuals. The majority of the pharmacological therapies for XP that are currently available focus on the disease's skin symptoms. In this review, we discuss how new treatments could be created using our existing understanding of the pathophysiology of XP help combat the symptoms of the nervous system. Furthermore, we turned our attention to potential novel pathways that target mitochondrial pathology because XP is associated with both neurodegeneration and malignancy.

Keywords : xeroderma pigmentosum, neurodegeneration and malignancy, neurological.

Introduction :
The autosomal recessive condition xeroderma pigmentosum (XP) is brought on by mutations in genes related to the DNA repair system. According to Kleijer et al. (2008), the incidence of XP is estimated to be 2.3 per million live births in Western Europe; however, Hirai et al. (2006) reports that XP is more common in other locations. XP can be categorized into clinically diverse complementation groups since eight causal proteins—XPA, XPB, XPC, XPD, XPE, XPF, XPG, and XPV—have so far been found (Bootsma and Hoeijmakers, 1991; Bowden et al., 2015). When DNA damage is present, the XPA to XPG proteins participate in various stages of the nucleotide excision repair (NER). Mutations in DNA polymerase η, which is involved in DNA synthesis, are present in patients with XP variant after damage caused by UV radiation (Lehmann et al., 1975; Masutani et al., 1999). Although additional symptoms, such as ophthalmological abnormalities and a propensity to cancers, are well recognized, the signs and symptoms of patients with XP can be broadly classified into cutaneous and neurological manifestations (Bradford et al., 2011; Brooks et al., 2013; Fassihi et al., 2016). The most comprehensive analysis of a cohort of XP patients to date has yielded precise clinical and molecular data, according to a study published recently by Fassihi et al. (2016). The research demonstrated how different types and locations of mutations in the causing genes determine the clinical variability of XP even among complementation groups (Fassihi et al., 2016).

Symptoms of dermatology and treatment approachesXP sufferers are united by the same trait of high UV radiation sensitivity. While not all individuals have this initial aberrant reaction to sunlight, it can cause severe scorching and blistering of the skin in babies (DiGiovanna and Kraemer, 2012; Sethi et al., 2013; Fassihi et al., 2016). However, all patients have startling changes in their skin that eventually lead to atrophy, telangiectasias, and areas of mixed hypo- and hyperpigmentation (Black, 2016). Early detection of premalignant lesions associated with complementation group, such as actinic keratoses and skin neoplasms in sun-exposed areas, is noted (DiGiovanna and Kraemer, 2012). According to Bradford et al. (2011), the most common skin tumors in XP patients are squamous and basal cell carcinomas, which are followed by malignant melanomas, which have an incidence rise of 10,000 and 2000 times, respectively. Remarkably, complementation groupings that exhibit Due to early detection and the implementation of sun protection measures, an aberrant acute sunburn reaction is linked to both neurodegeneration and a decreased incidence of skin cancer (Sethi et al., 2013; Fassihi et al., 2016).

The interdisciplinary clinical therapy of XP patients mostly concentrates on rigorous UV protection and treatment of

malignancies in the absence of particular medicines that target the underlying failure of DNA repair (Tamura et al., 2014). According to Moriwaki et al. (2017), the former includes minimizing sunlight exposure by wearing UV-protected long sleeves, installing window filters on vehicles and buildings, and applying sunscreen lotions with the greatest available protective filters. Frequent skin cancer screening is necessary to identify cancers early on, and those that are treated using the same protocols as non-XP patients (Naik) (2013), et al. Surgical excision is the first-line treatment. However, case studies on conservative treatments have shown favorable outcomes with topical administration of 5-fluorouracil (Lambert and Lambert, 2015) and imiquimod 5% (Malhotra et al., 2008; Yang et al., 2015). Using a liposome formulation containing the bacterial DNA repair enzyme T4N5 endonuclease, a prospective randomized controlled experiment revealed a lower incidence of actinic keratoses and basal cell carcinomas (Yarosh et al., 2001). Subsequent research, however, was abandoned because it was ineffective.neurological symptoms and the absence of a causal intervention
Neurodegeneration is not uniformly prevalent throughout the complementation groups, and it is most frequently linked to XPA and XPD, with XPB, XPG, and XPF following (Anttinen et al., 2008; Niedernhofer et al., 2011; Karass et al., Fassihi et al., 2016; 2015). In all, neurological impairment of varying degree affects 25–30% of XP patients in North America and Europe. 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, are experienced by affected patients due to the progressive cerebral and cerebellar degeneration with frequent involvement of the peripheral nervous system (Rass et al., 2007; Niedernhofer, 2008; Lehmann et al., 2011; Fassihi et al., 2016). According to Bradford et al. (2011), patients with neurodegeneration had a mean age of death of 29 years, while patients without neurodegeneration had a mean age of 37 years.

The neurological symptoms of XP currently have no known therapeutic treatment, and symptoms are handled with encouraging actions. Although UV-B radiation exposure has a critical role in the development of epidermal carcinogenesis in XP, nothing is known about the cause of the neurological symptoms. It has been discovered recently that NER is necessary for the repair of certain endogenous DNA lesions caused by reactive species production, in addition to UV radiation damage (see Brooks, 2017). These lesions are caused by 8,5-cyclopurine deoxynucleotides (cyPu), which are created when hydroxyl radicals react with DNA.

According to studies by Tomas Lindahl (Kuraoka et al., 2000) and Jay Robbins (Brooks et al., 2000), cyPu are exclusive substrates for NER, indicating that mutations in this particular DNA repair pathway may be a factor in the neurological symptoms seen by individuals with XP (see Brooks, 2017). A deeper comprehension of the etiology of neurological impairment, which will be covered in more detail throughout the review, and it appears to be essential for the creation of causal treatments**.**

Associated illnesses
Cockayne syndrome (CS) is the NER condition most closely related to XP. According to Spivak (2004), CS-A patients have mutations in the ERCC8 gene, whereas CS-B patients have mutations in the ERCC6 gene. According to Kamenisch et al. (2010), the CS-A and CS-B proteins are necessary for transcription-coupled-NER, a sub-branch of NER that quickly fixes damage to the transcribed strand of actively transcribed genes. According to Wang et al. (2014), they also play a part in transcription and neural differentiation. According to Kraemer et al. (2007), CS shares similarities with XP's neurological phenotype, which is comparatively milder, in terms of development and neurological phenotype. Progressive spasticity, peripheral neuropathy, ataxia, weakness, and dementia are examples of neurological symptoms Both a failure in brain growth and a progressive loss of neurons underlie these abnormalities. CS is not linked to a higher incidence of skin cancers, despite the fact that patients are photosensitive (Rapin et al., 2006). All patients have a significantly shorter life expectancy, albeit this varies depending on the clinical subtype (Rapin et al., 2006). A rare neurodegenerative condition known as "XP-CS complex" includes the clinical traits of both XP and CS. Patients experience the cutaneous symptoms associated with XP in addition to growth retardation and neurological deterioration (Natale and Raquer, 2017). Despite having distinct genetic flaws, CS and XP are similar in that they have deficient NER and are cellularly hypersensitive to UV light, as will be covered in more detail below.

Additional illnesses that are similar in terms of clinical and molecular Both a failure in brain growth and a progressive loss of neurons underlie these abnormalities. CS is not linked to a higher incidence of skin cancers, despite the fact that patients are photosensitive (Rapin et al., 2006). All patients have a significantly shorter life expectancy, albeit this varies depending on the clinical subtype (Rapin et al., 2006). A rare neurodegenerative condition known as "XP-CS complex" includes the clinical traits of both XP and CS.

Patients experience the cutaneous symptoms associated with XP in addition to growth retardation and neurological deterioration (Natale and Raquer, 2017). Despite having distinct genetic flaws, CS and XP are similar in that they have deficient NER and are cellularly hypersensitive to UV light, as will be covered in more detail below Axonal neuropathy (AOA1; AOA2; Clements et al., 2004); ataxia with oculomotor apraxia type 1 (iii); spinocerebellar ataxia with axonal

neuropathy (SCAN1; El-Khamisy et al., 2005; Gilmore, 2014) (v) and Riddle syndrome (Stewart et al., 2009), which share some neurological features like ataxia and have underlying DNA repair defects. While the genetic origin of cancer in XP is known, the pathophysiology of neurodegeneration remains unclear. A common pathophysiological aspect of all these illnesses is mitochondrial dysfunction (Le Ber et al., 2007; Scheibye-Knudsen et al., 2013).

Pathophysiology

Damage from oxidation in XP Neurodegeneration is primarily caused by oxidative stress and accumulated oxidative DNA damage in neurons (Hayashi, 2009; Niedernhofer et al., 2011). Neurons are sensitive to changes in energy metabolism because they have a high metabolic burden (Rothe et al., 1993). Increased production of ROS is a result of high oxygen consumption (Hayashi, 2009). Numerous forms of oxidative DNA damage can arise from endogenous genotoxic mechanisms, including aberrant oxidative cellular metabolism and the production of reactive oxygen species (ROS), which can also compromise cell integrity. The majority of this damage, including oxidized purines and pyrimidines, single-strand breaks, and other damage, is repaired by XP-independent mechanisms including base excision repair. But as previously mentioned, some forms of oxidative damage, such cyclopurines, can are believed to accumulate in XP since they can only be fixed by NER (Brooks et al., 2000; Kraemer et al., 2007; Brooks, 2008). In terminally developed post-mitotic cells like neurons, this unrepaired oxidative DNA damage builds up over time and negatively impacts transcription and apoptosis regulation, ultimately leading to neurodegeneration.

By raising ROS levels, affecting oxidative phosphorylation (OXPHOS) and cell energy metabolism through oxidative damage to the electron transport chain (ETC) subunits and membrane phospholipids, silencing the genes that produce the NER proteins, CSA, CSB, XPA, and XPC, modifies redox homeostasis (Parlanti et al., 2015; Brennan-Minnella et al., 2016). As a result, oxidative stress increases even more (Kowaltowski and Vercesi, 1999). Additionally, XPC down-regulation led to a rise in oxidative nuclear and mitochondrial OXPHOS is hampered by DNA (mtDNA) damage (Pascucci et al., 2011). But NER is absent from mtDNA, and base excision repair is mostly responsible for repairing damage (Wilson and Bohr, 2007; Boesch et al., 2011).

According to Fang et al. (2014), the lack of NER proteins in mitochondria implies that nuclear disruptions and the faulty signaling pathways they cause come before mitochondrial abnormalities. Furthermore, XP's clinical heterogeneity suggests that pathogenic processes go beyond the ineffective repair of DNA lesions that affect helix structure. Thus, oxidative stress due to non-DNA repair may have a role in the aetiology of cancer and neurodegeneration in XP. It could be involved in a wide range of activities, both causing and being caused by numerous interrelated pathogenic processes, the direction of which is hard to pinpoint.

XP's mitochondrial malfunction Mitochondrial OXPHOS is hampered by DNA (mtDNA) damage (Pascucci et al., 2011). But NER is absent from mtDNA, and base excision repair is mostly responsible for repairing damage (Wilson and Bohr, 2007; Boesch et al., 2011).

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XP's mitochondrial malfunctionmitochondrial (2010) Plun-Favreau et al. Because ROS are produced during regular cell metabolism and play significant roles in cell signaling for growth and metabolism (Jezek and Hlavata, 2005; Valko et al., 2007), they are strictly regulated. Changed energy states in the ETC are linked to elevated ROS levels (Jezek and Hlavata, 2005). The cell suffers from increased ROS generation and increased electron leakage caused by ETC malfunction (Koopman et al., 2010). Although ROS-induced oxidative stress is probably the main cause of cell death, ROS can also directly induce apoptosis through death-receptor activation and caspases-8 and -3 (Kulms et al., 2002). Furthermore, ROS formation increases and has negative effects when it is not effectively counteracted by the body's own antioxidant systems regarding proteins, fats, and DNA (Cooke et al., 2003; Hayashi, 2009). Primary defense against oxidative stress is provided by detoxifying enzymes including glutathione peroxidase, SOD, and catalase, as well as antioxidants like glutathione and coenzyme Q10 (CoQ10) that neutralize ROS (Barrientos et al., 2009). The causes of mitochondrial malfunction in XP remain unclear. XP-A, XP-D (Arbault et al., 2004; Arczewska et al., 2013; Parlanti et al., 2015), and XP-C patient cells have been shown to generate ROS at high and sustained levels (Frechet et al., 2008). Furthermore, antioxidant levels in XP-patient cells are abnormally low (Nishigori et al., 1989; Vuillaume et al., 1992).

Patients with CS-B and mitochondrial dysfunction

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In CS models, the mitochondrial deficiency has also been seen as secondary, however it has been shown that the CS-B protein localizes to the mitochondria, indicating that this protein may play a part in the repair of mtDNA (Arnold et al., 2012). The cells lacking CS-B exhibited elevated levels of mitochondria, free radicals and Ψm, as well as an increase in oxygen consumption (Osenbroch et al., 2009; Cleaver et al., 2014).
The transcription factors PGC-1α, TFAM, and ERRα—which are associated with mitochondrial biogenesis—were not changed in CS-B-deficient cells, suggesting that these alterations were not caused by an increase in mitochondrial biogenesis. Because biogenesis and degradation determine the quantity of mitochondria, Scheibye-Knudsen et al. (2012) looked into the possibility of autophagy suppression.

Intriguingly, they discovered that in CS-B-deficient cells, stress reduced the co-localization of LC3, P62, and suppression of autophagy, which explains the mitochondrial phenotype. By administering rapamycin to these cells, the scientists were also able to induce autophagy and reverse the phenotypic (this will be covered in more detail later in the text). Additionally, rapamycin appears to be neuroprotective, which means it may lessen the disease's neurological symptoms (Bove et al., 2011; Dello et al., 2013). This is in line with the discovery that XPA-deficient cells have reduced autophagy, which raises the amount of mitochondria in the cell and may be a factor in the neurodegenerative phenotype these patients exhibit (Fang et al., 2014)**.**

Possible pharmaceutical strategies
CoQ10-based antioxidant treatment
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). age (Muller et al., 2007; Bohr et al., 1998), CoQ10 was looked into as a possible treatment approach. However, since CoQ10 levels seem to be constant throughout time in both the illness and control groups, these changes cannot be explained by changes in CoQ10 levels (Duncan and Heales, 2005). In mononuclear cells (MNCs) from XP patients, there was a trend toward a decreased level of CoQ10 concentrations with age in our XP cohort of patients (XPA, XPD, XPF, and XPG) with variable neurological phenotype (Giunti, personal communication). However, the lower levels remained within the normal range. This could indicate a potential decrease with aging, but not with the degree of the phenotypic. In contrast, Tanaka et al.'s (1998) findings show a pathologically low CoQ10 plasma level that was associated with the advancement of the illness (Tanaka et al., 1998). Tanaka et al.'s neurological phenotype, however, was severe, and the patients' ages ranged from 3 to 25 years, which is noticeably younger than the mean of 34 years in our group (range 5–46 years). We can explain the discrepancy between the two research' results for all of this. Additionally, two distinct assays were used to assess the CoQ10 levels in MNCs and plasma.

Interestingly, none of the complementation groups' XP plasma samples showed a decrease in CoQ10 with age. However, we discovered that XPC (cancer-prone) and XPD (severe neuropathology) complementation groups differed in the amount of CoQ10 that fibroblasts had XPD fibroblasts had a far lower concentration than XPC fibroblasts, whose levels were comparable to those of controls. This suggests that CoQ10 supplementation might be advantageous for neurodegenerative XP complementation groups. The insolubility of CoQ10 makes it difficult to treat CoQ10 deficiency and ETC disorders with CoQ10 supplementation (Hargreaves, 2014). However, a non-randomized study mentioned above suggested that a daily oral dose of 0.9–1.5 mg·kg−1 improves daily activity in a subset of XP patients (Tanaka et al., 1998). Tanaka et al. did not give information about complementation groups, so it is unclear if patients with neurological involvement made up the majority of this grouping.

One of our cohort's XPF patients had a trial on CoQ10 (180 mg·day−1) started because of persistent weariness.
but over the course of three years had no positive impact on this symptom or the Scale for the Assessment and Rating of Ataxia rating scale (Giunti, personal communication). Trials that are randomized controlled are required to assess the effectiveness of CoQ10 supplementation in individuals with XP.

Rapamycin-based autophagy stimulation therapy
Increasing autophagy is a new treatment option to prevent neurodegeneration. According to Mizushima and Komatsu (2011), this physiological activity is in charge of eliminating misfolded protein aggregates and cellular organelles, which supports the preservation of cellular integrity and homeostasis. According to studies by Scheibye-Knudsen et al. (2012) and Fang et al. (2014), autophagy is a dynamic recycling system that appears to be down-regulated in neurodegeneration generally and in CS and XPA in particular. Autophagy is induced by rapamycin by selectively inhibiting the mechanistic target of rapamycin kinase (mTOR). While this can limit cell survival and proliferation, it has no effect on neurons because rapamycin has been shown to be helpful in neurodegeneration. For instance, rapamycin-induced autophagic stimulation has been linked to up-regulation of postsynaptic protein 95, synapsin I, and synaptophysin in Alzheimer's dementia (AD),

the most prevalent neurodegenerative illness (Anttinen et al., 2008; Singh et al., 2017). These proteins are essential for maintaining synaptic integrity and are down-regulated in AD. Additionally, there was a decrease in oxidative stress, which is a sign of AD. Above all, phase II clinical trials for rapamycin are presently being conducted for similar but distinct neurodegenerative illnesses, including Huntington disease and amyotrophic lateral sclerosis**.**

Amitriptyline-based neurite development therapy

One more Amitriptyline, a tricyclic antidepressant with a licence to treat depression and neuropathic pain, is one such tactic. Wang et al. (2016) tried to address this by using amitriptyline to enhance neurite formation in cellular models of CS-B. This was because the neuropathophysiological of CS-B is characterized by aberrant neuronal development (unlike XP neurons that undergo normal development but degenerate later in adulthood). Furthermore, they showed that neurite growth was restored by up-regulating the normally suppressed cascade including synaptotagmin-9 (SYT-9) (Wang et al., 2016). Furthermore, one of the pharmaceuticals that enhanced neurite development and up-regulated tropomyosin receptor kinase B (TrkB) was amitriptyline (Wang et al., 2016). SYT-9 is a major modulator of abnormal neuronal development in CS-B It inhibiting the growth of neurites in knockdown CS-B neurons by being down-regulated (Wang et al., 2016). According to Dean et al. (2012), a family of proteins known as the SYT family controls membrane fusion and trafficking. Yoshihara and Montana (2004) noted that SYT-1, -2, and -9 in particular are calcium sensors on synaptic vesicles and are important in synaptic vesicles membrane fusion events. Neurite proliferation was restored in CS-B models by upregulating SYT-9. Pharmacological tests with amitriptyline, which efficiently up-regulates TrkB, supported this (Wang et al., 2016). Brain-derived neurotrophic factor, which breaks down more quickly than amitriptyline and is unstable in cultures, also has an impact similar to this one. Nevertheless, apart from this compound's advantageous effect on neurite development, amitriptyline also seems to stimulate mitochondrial fragmentation in Parkinson's disease neural models (Lee et al., 2015). Antioxidants may be added to the treatment regimen to mitigate this effect, which would need to be carefully evaluated against any potential advantages**.**

In conclusion

In conclusion, even though there are currently no pharmaceutical treatments for the neurological symptoms associated with XP, we have covered some potential treatment options that are being researched in order to lessen these symptoms. We emphasized the potential contribution of CoQ10 antioxidant therapy to reducing the oxidative stress caused by mitochondrial malfunction, which follows NER deficiency. Additionally, we suggested that rapamycin may be used to reactivate the autophagic machinery that is down-regulated in CS and XPA, and that amitriptyline could be used to stimulate neurite formation in order to rebuild synaptic connections simultaneously therapy will be provide were patients are easily recover it were drug give pharmacological action both Parkinson and Alzheimer.

Conflict of interest

The authors declare no conflicts of interest.

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