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Spinocerebellar Ataxia with Axonal Neuropathy (SCAN1): A Disorder of Nuclear and Mitochondrial DNA Repair

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1. Introduction

Spinocerebellar ataxias (SCAs) are a group of progressive and irreversible neurological diseases affecting gait and movement coordination. Many result from cerebellar degeneration or the impairment of a portion of the neuroaxis that contributes to cerebellar inflow or outflow (Embirucu et al., 2009). In the cerebellum, the dysfunction and death of Purkinje cells, granule cells or interneurons can cause SCA. Molecular mechanisms for this pathology include polyglutamine tract expansion (SCA1, SCA2, SCA3), flawed basal transcription (SCA17) and defective DNA repair (ataxia telangiectasia, spinocerebellar ataxia with axonal neuropathy (SCAN1) and ataxia with oculomotor apraxia type 1) (Hire et al., 2010).

The mechanism by which defective DNA repair causes neuronal dysfunction and death is not yet fully understood, but damage to the nuclear and mitochondrial genomes underlie each potential explanation. Dysfunction of nuclear DNA repair enzymes results in nuclear DNA damage that impedes transcription and also induces programmed neuronal death (Fishel et al., 2007). Dysfunction of mitochondrial DNA repair enzymes leads to mitochondrial DNA damage that impairs mitochondrial gene expression causing mitochondrial dysfunction, oxidative stress and subsequently programmed neuronal death (Bender et al., 2006). Accumulation of DNA breaks within the neuronal nuclear genome has also been proposed to initiate expression of cell-cycle activators as a cellular response to repair genomic damage through replication-dependent mechanisms; however, these neurons are frequently unable to establish a new G0 quiescent state and this in turn activates neuronal death mechanisms (Kruman et al., 2004). Lastly, besides direct affects on the neurons, defective DNA repair also indirectly induces neuronal death by causing dysfunction of glia, which have trophic interactions with neurons and modulate neurotransmitter levels at synapses (Barzilai, 2011; Lobsiger and Cleveland, 2007).

For the purposes of this review, we focus on SCAN1, an autosomal recessive DNA repair disorder caused by the p.His493Arg active site mutation in tyrosyl-DNA phosphodiesterase 1 (Tdp1), an enzyme that enables DNA repair by processing blocked 3' DNA termini. This mutation impairs this activity and also predisposes to the formation of Tdp1-DNA adducts.

Since the loss of Tdp1 activity predisposes to both nuclear and mitochondrial DNA damage, this review focuses on understanding SCAN1 etiology from the perspectives of DNA repair and mitochondrial dynamics.

2. Spinocerebellar ataxia with axonal neuropathy (SCAN1)

The only reported SCAN1 patients are from an extended Saudi Arabian family having nine affected individuals (Takashima et al., 2002). SCAN1 is characterized by normal intelligence and a late-childhood onset progressive cerebellar ataxia and peripheral neuropathy. Initial features include ataxic gait, gaze nystagmus and cerebellar dysarthria. As the disease advances, the affected individuals develop impaired pain, vibration and touch sensation in the hands and legs and eventually a steppage gait and pes cavus. With further progression of their cerebellar, motor and sensory symptoms, affected individuals become wheelchair-dependent in early adulthood (Hirano et al., 1993). Magnetic resonance imaging studies show cerebellar atrophy, especially of the vermis (Takashima et al., 2002). Nerve conduction studies show decreased amplitudes characteristic of axonal neuropathy. These clinical findings suggest a disease of large, terminally differentiated, post-mitotic neurons, especially those of the cerebellum, dentate nuclei, anterior spinal horn and dorsal root ganglia.

Currently, there are only symptomatic treatments for SCAN1. Physical therapy is recommended for maintaining activity. Prostheses, walking aids and wheelchairs are recommended for improving mobility. In addition, based on studies of cells from SCAN1 patients and animal models, SCAN1 patients should avoid exposure to genotoxic agents such as camptothecin, irinotecan, topotecan, bleomycin and radiation (Hirano et al., 2007).

Clinically, SCAN1 can be considered in the differential diagnosis for individuals who have 1) a slowly progressive cerebellar ataxia with onset in late-childhood or adolescence, 2) peripheral axonal neuropathy, 3) no signs of oculomotor apraxia and 4) no evidence of extraneurologic features such as telangiectasias, cancers or immunodeficiency. Supportive findings include increased serum cholesterol and decreased serum albumin (Takashima et al., 2002). The only known genetic defect causing SCAN1 is the c.1478A>G mutation in *TDP1*. This missense mutation, which encodes the p.His493Arg amino acid alteration, can be detected by DNA sequencing or by digestion of the PCR product with *BsaAI* (Hirano et al., 2007; Takashima et al., 2002).

3. DNA repair mechanisms and progressive neurodegeneration

As exemplified by SCAN1, many DNA repair defects cause progressive neurodegenerative disease (Table 1) (Barekati et al., 2010; Sahin and Depinho, 2010). Neurons are particularly vulnerable to the accumulation of unrepaired DNA lesions because they are long-lived, post-mitotic and not readily replaced.

DNA lesions arise as a consequence of endogenous or exogenous genotoxic insults. However, the seclusion of central neurons, which are frequently more severely affected than peripheral neurons, by the blood-brain barrier suggests that the DNA lesions arise predominantly from endogenous genotoxic insults, particularly the oxidative damage arising from mitochondrial dysfunction (Harman, 1972, 1981)

Repair of DNA lesions is mediated by four major DNA repair pathways: double-strand break repair (DSBR), mismatch repair (MMR), nucleotide excision repair (NER), and base excision repair (BER). DSBR corrects double-strand breaks (DSB) in the DNA backbone; MMR corrects mismatches of normal bases; NER repairs bulky helix distorting DNA lesions, and BER repairs damage to a single nucleotide and handles single-strand DNA breaks (SSB). Dysfunction of each of these DNA repair processes causes or has been associated with progressive neurodegenerative disease (Table 1) (Jeppesen et al., 2011).

Gene(s)	DNA Repair Defect	Clinical Syndrome	Main Symptoms
SETX	Defective DSBR	Ataxia with oculomotor apraxia type 2	Cerebellar atrophy Axonal sensorimotor neuropathy Oculomotor apraxia Elevated serum concentration of alpha-fetoprotein
ATM	Defective DSBR	Ataxia telangiectasia	Progressive ataxia Defective muscle coordination Dilation of blood vessels in skin and eyes Immune deficiency Predisposition to cancer
MRE11	Defective DSBR	Ataxia telangiectasia-like	Slowly progressive cerebellar ataxia Ionizing radiation hypersensitivity
XPA, XPF, XPG, POLH, ERCC1-4, DDB2	Defective NER	Xeroderma pigmentosum	Sensitivity to sunlight Slow neurodegeneration Skin cancer
ERCC6, ERCC8	Defective NER and TC-NER	Cockayne's Syndrome	Sensitivity to sunlight Growth retardation Neurological impairment Progeria
ERCC2, ERCC3, GTF2H5	Defective NER	Trichothiodystrophy	Sensitivity to sunlight Dystrophy Short brittle hair with low sulfur content, Neurological and psychomotoric defects
TDP1	Defective BER	Spinocerebellar ataxia with axonal neuropathy 1	Progressive degeneration of post-mitotic neurons
APTX	Defective BER	Ataxia with oculomotor apraxia type 1	Slowly progressive cerebellar ataxia, followed by oculomotor apraxia Severe primary motor peripheral axonal motor neuropathy
ALS2, SETX, SOD1, VAPB	Defective BER	Amyotrophic lateral sclerosis	Progressive degeneration of motor neurons Muscle weakness and atrophy
C10orf2	Defective mitochondrial DNA repair	Infantile-onset spinocerebellar ataxia	Muscle hypotonia Loss of deep-tendon reflexes Athetosis

Table 1. DNA repair enzymes with mutations causing neurodegenerative disease. NER: Nucleotide excision repair, TC-NER: Transcription-coupled nucleotide excision repair, MMR: Mismatch repair, BER: Base excision repair, DSBR: Double-strand break repair, (Embirucu et al., 2009; Katyal and McKinnon, 2007; Subba Rao, 2007)

3.1 Double-strand break repair

DSBR corrects DNA double-strand breaks (DSBs) induced by exogenous sources such as ionizing radiation and genotoxic compounds or by endogenous sources such as reactive oxygen species, replication fork collapse, and errors of meiotic recombination (Ciccia and Elledge, 2010). The two major DSBR pathways in mammalian cells are homologous recombination (HR) and non-homologous end-joining (NHEJ). HR allows high fidelity repair of DSBs during DNA replication by using the intact sister chromatid as a template, whereas NHEJ allows for the error-prone repair of DSBs by modifying and ligating the two DNA termini of a DSB without using an undamaged template. HR is restricted to the late S to G2/M phase of the cell cycle when a sister chromatid is available in proliferating cells, whereas NHEJ operates throughout the cell cycle and can repair DSBs in differentiated cells. Therefore, since the mature nervous system is predominately post-mitotic cells, NHEJ is the major DSBR pathway in the postnatal brain.

Two NHEJ disorders with progressive neurodegeneration of the postnatal brain are ataxia telangiectasia and ataxia telangiectasia-like disorder. The neurological symptoms of ataxia telangiectasia are an early childhood onset of ataxia that generally leads to wheel chair dependence before adolescence. The neurological symptoms of ataxia telangiectasia-like disorder are similar to those of ataxia telangiectasia but of later onset and slower progression. For both disorders, the neurodegeneration is characterized by the loss of cerebellar granule and Purkinje cells.

3.2 Mismatch repair

MMR removes base-base mismatches and insertion-deletion loops that arise during DNA replication and recombination. Base-base mismatches are created when errors escape DNA polymerase proofreading, and insertion-deletion loops arise when the primer and template strand in a microsatellite or repetitive sequence dissociate and re-anneal incorrectly causing the number of microsatellite-repeat units in the template and in the newly synthesized strand to differ. Interestingly, expression of MMR components is not limited to replicating cells but is also observed in non-replicating postnatal neurons suggesting that this pathway plays a role in maintaining the genomic integrity of differentiated cells too (Ciccia and Elledge, 2010).

Consistent with a function in differentiated cells, studies of the Huntington trinucleotide repeat (CAG) in mice have shown somatic age-dependent repeat expansion that is suppressed by deficiency of some MMR components and is triggered by DNA glycosylases of the BER pathway (Kovtun et al., 2007; Owen et al., 2005). The relevance of the MMR pathway to trinucleotide repeat expansions of the human neurological disorders remains undefined however.

3.3 Nucleotide excision repair

In human cells, recognition of bulky helix distorting DNA lesions leads to the removal of a short single-stranded DNA segment surrounding and including the lesion. This creates a single-strand gap in the DNA that is subsequently filled during repair synthesis by a DNA

polymerase using the undamaged strand as a template. NER can be divided into two sub-pathways, global genomic NER (GG-NER) and transcription-coupled NER (TC-NER). GG-NER and TC-NER differ in the recognition of the DNA lesion but subsequently use the same excision mechanism. GG-NER recognizes and repairs DNA lesions anywhere in the genome, whereas TC-NER only resolves lesions in the actively transcribed DNA strand (de Laat et al., 1999).

Two NER-associated disorders, xeroderma pigmentosum and Cockayne syndrome, feature progressive neurodegeneration (Kraemer et al., 1987). About 30% of xeroderma pigmentosum patients have neurological symptoms that include abnormal motor control, ataxia, peripheral neuropathy, dementia, brain and spinal cord atrophy, microcephaly and sensorineural deafness. In contrast, nearly all Cockayne syndrome patients have progressive neurological disease characterized by demyelination in the cerebral and cerebellar cortex, calcification in the basal ganglia and cerebral cortex, neuronal loss, sensorineural hearing loss and decreased nerve conduction (Nance and Berry, 1992). The progressive neurodegeneration in both xeroderma pigmentosum and Cockayne syndrome are attributable to apoptotic cell death (Lehmann, 2003).

3.4 Base excision repair

BER corrects the most common forms of DNA damage by recognizing, excising and replacing a broad spectrum of specific forms of DNA modifications including those arising from deamination, oxidation and alkylation. It is initiated by a distinct lesion-specific mono- or bi-functional DNA glycosylase and completed by either of two sub-pathways: short-patch BER (SP-BER) that replaces one nucleotide or long-patch BER (LP-BER) that replaces 2–13 nucleotides (Frosina et al., 1996).

The BER proteins are also responsible for repairing DNA SSBs. SSBs are some of the most common lesions found in chromosomal DNA and arise via enzymatic cleavage of the phosphodiester backbone or from oxidative damage or ionizing radiation. Examples of enzymatic cleavage causing SSBs include those arising during BER (Connelly and Leach, 2004) and during DNA topoisomerase I (Topo I) activity (Pommier et al., 2003).

Ataxia with oculomotor apraxia type 1 and SCAN1 are both associated with defects in the repair of SSBs, specifically the processing of obstructive termini (Table 1). The neurodegenerative features of ataxia with oculomotor apraxia type 1 include progressive cerebellar atrophy, late axonal peripheral motor neuropathy, ataxia and oculomotor apraxia. The features of SCAN1, which is caused by a mutation of *TDP1*, have been described above.

4. Tdp1 function

TDP1 encodes tyrosyl-DNA phosphodiesterase 1 (Tdp1), a 608 amino acid enzyme that contains a bipartite nuclear localization sequence and two conserved HxKx4Dx6G (G/S) HKD (histidine-lysine-arginine) signature motifs. The two HKD motifs form a single symmetrical active site characteristic of the phospholipase D superfamily and catalyze a phosphoryl transfer that is common to enzymes in this superfamily (Interthal et al., 2001). The HKD motifs are very important for the catalytic function of Tdp1. Tdp1 enables SSBR

and DSBR by removing obstructing compounds linked by a phosphodiester bond to DNA 3' termini and complements the 5'-phosphodiesterase function of TTRAP (Tdp2) (Cortes Ledesma et al., 2009; el-Khamisy and Caldecott, 2007; Zhou et al., 2009). Tdp1 endogenous substrates include 3' tyrosine-DNA phosphodiester moieties, phosphoglycolates, mononucleosides and tetrahydrofurans, and exogenous substrates include 4-methylphenol, 4-nitrophenol and 4-methylumbelliferone (Figure 1) (Dexheimer et al., 2008; Interthal et al., 2005a). Tdp1 has the highest affinity for the 3' tyrosine-DNA phosphodiester moieties, which are characteristic of Topo I-DNA intermediates (Dexheimer et al., 2010).

Fig. 1. Substrates of Tdp1. Tdp1 can remove both physiologic substrates and non-physiologic substrates. R = Substrates.

During repair, replication, transcription, recombination and chromatin remodeling, Topo I relaxes superhelical tension by nicking DNA to allow controlled rotation of the broken DNA strand around the intact strand. After DNA relaxation has occurred, a nucleophilic attack by the DNA 5' hydroxyl group on the phosphotyrosyl linkage between Topo I and the 3' end of the DNA at the nick usually religates the DNA, and the Topo I dissociates. However, DNA damage such as abasic sites, nicks, and mismatched base pairs frequently impede removal of Topo I from the DNA by causing a misalignment of the 5' hydroxyl end of the DNA that prevents it from acting as a nucleophile. (Pommier et al., 1998; Pommier et al., 2003; Pourquier and Pommier, 2001) Additionally, the 3'-Topo I-DNA intermediate can become unduly long-lived if Topo I binds oxidative base lesions (Interthal et al., 2005b). These trapped or long-lived Topo I-DNA covalent intermediates can then be converted to irreversible DNA breaks when the DNA replication machinery or RNA polymerase collides with the Topo I-DNA complex (Hsiang et al., 1989; Tsao et al., 1993; Wu and Liu, 1997)

Clearance of the trapped or stalled 3'-Topo I-DNA intermediates occurs via SSB or DSB if the SSB is converted to a DSB by collision of the DNA replication machinery with the trapped or stalled 3'-Topo I-DNA intermediate. Following recognition of the break, the trapped or stalled Topo I is proteolytically cleaved leaving a peptide bound to the 3' end of the DNA by the phosphodiester bond formed between the DNA and the Topo I active site

tyrosine (Tyr723). Tdp1 then acts on the phosphodiester bond and removes the obstructing Topo I peptide from the 3' terminus (Debethune et al., 2002; Liu et al., 2002). The Tdp1 reaction removes the peptide from the DNA by an S_N2 nucleophilic attack of His263, which resides in the first HKD motif, on the phosphodiester bond; Tdp1 is then released from the DNA by the catalytic activity of His493, which resides in the second HKD motif (Figure 2).

Fig. 2. Mechanism of Tdp1 catalytic activity. (A) Wild type Tdp1 removes proteolysed Topo I and forms a covalent intermediate with DNA before His493 of the second HKD motif excises Tdp1 from DNA through a nucleophilic substitution. (B) In SCAN1, the mutated Tdp1 (p.His493Arg) removes proteolysed Topo I but remains trapped on DNA and leads to accumulation of Tdp1-DNA adducts.

4.1 Tdp1 and nuclear DNA repair

Within the nucleus, Tdp1 is a component of the SSB multi-protein repair complex containing PARP1, LIG3 α , XRCC1 and PNKP (Das et al., 2009). This repair complex is activated after proteasomal degradation of stalled Topo I (Zhang et al., 2004). PARP1 is an important regulator of the SSBR/BER pathway as it enhances the recruitment of DNA repair proteins. PARP1 hydrolyzes NAD⁺ to catalyze the synthesis of ADP-ribose units onto glutamate

Fig. 3. Tdp1-dependent and Tdp1-independent pathways for the removal of Topo I-DNA covalent complexes. After Topo I is trapped on the DNA, proteolysis of Topo I occurs. The remaining Topo I peptide can be removed by either Tdp1-dependent pathway or Tdp1-independent pathways. Topo I* = Topo I peptide.

molecules of acceptor proteins. The addition of poly-ADP ribosyl (PAR) polymers onto histones promotes the relaxation of chromatin, while SSB proteins such as XRCC1 and Lig3a are electrostatically attracted to PAR and are thus recruited to the site of DNA damage (El-Khamisy et al., 2003; Krishnakumar and Kraus, 2010). It is thought that XRCC1 acts as a molecular scaffold for the binding of Tdp1 and Lig3a and stabilizes the enzyme complex in the processing of Topo I derived SSBs. Processing of the 3' tyrosine-DNA phosphodiester moieties by Tdp1 leaves a 3'-P terminus that is converted to 3'-OH by the phosphatase action of PNKP. The kinase activity of PNKP phosphorylates the 5'-OH terminus, allowing gap filling by DNA polymerase β (Pol β), and finally the DNA nick is sealed by lig3a with the aid of the XRCC1 scaffold (Figure 3).

How Tdp1 processes obstructing 3' overhangs on DNA DSBs has not been fully defined. The dependence of Tdp1 processing of DSB termini on the autophosphorylation activity of the NHEJ component DNA-PK suggests that Tdp1 contributes within the NHEJ pathway and that DNA-PK modulates the accessibility of DNA ends enabling Tdp1 to accomplish the processing necessary for eventual end-joining (Zhou et al., 2009).

One redundant DNA repair activity for Tdp1 is the nucleolytic removal of several DNA bases beginning upstream of the stalled Topo I. This is mediated by 3'-flap endonuclease complexes in the nucleus such as Mus81-MMS4 and XPF-ERCC1 that cleave at the 3'-flap created by stalled Topo I to enable short-patch gap filling. In comparison to Tdp1 processing, however, this mechanism is error-prone and less efficient.

4.2 Tdp1 and mitochondrial DNA repair

Besides its role in the repair of nuclear DNA, Tdp1 also plays a role in mitochondrial DNA (mtDNA) repair (Das et al., 2010). Mitochondria are membrane-enclosed organelles that generate most of the ATP via the electron transport chain at the inner mitochondrial membrane. This process leads to the generation of reactive oxygen species, and while mitochondria have various antioxidant enzymes to deactivate these highly reactive molecules, they do not constitute a perfect defense. This inevitably exposes the mtDNA to high levels of oxidative stress, particularly since the mtDNA is located in close proximity to the inner mitochondrial membrane and lacks protective histones (Ames et al., 1993). Consequently, the levels of oxidative base damage in mitochondrial DNA are 2–3 fold higher compared to nuclear DNA (Hudson et al., 1998), and the damage is more extensive and persistent than in nuclear DNA (Yakes and Van Houten, 1997).

Several DNA repair activities and pathways that function in the nucleus have also been identified and characterized in mammalian mitochondria. These include BER, MMR, and some components of DSBR (Larsen et al., 2005). Given the prevalence of small lesions generated by oxidative stress in the mitochondria, BER is the predominant mtDNA repair pathway. Mitochondrial BER proteins are not encoded by the mitochondrial genome; rather they are mitochondrial versions of nuclear-encoded proteins (Larsen et al., 2005). Among these is Tdp1, which could participate in the repair of oxidative mitochondrial DNA damage via resolution of 3'-phosphoglycolate obstructive termini and processing the apurinic/apyrimidinic (AP) sites arising from the DNA glycosylase removal of DNA lesions such as 7,8-dihydro-8-oxoguanine (8-oxoG). These two abilities of Tdp1 are also shared by APE1, although the relative contribution of each protein to either process is unclear.

Additionally, as there is a mitochondrial Topo I (mtTopo I) that has 71% identity and 87% similarity with the nuclear Topo I (Zhang et al., 2001), we hypothesize that the high level of mtDNA lesions predisposes to generation of long lived or trapped mtTopo I-DNA complexes similar to those in the nucleus and that the removal of mtTopo I peptides from mtDNA is also a function of mitochondrial Tdp1.

5. The molecular basis of SCAN1

In SCAN1, the p.His493Arg mutation in the second HKD motif of Tdp1 affects the active site of the protein and reduces its catalytic activity by 25-fold (Interthal et al., 2005b; Takashima et al., 2002). This alteration both decreases the processing of Topo I-DNA adducts and impairs the intermolecular reaction that would ordinarily release Tdp1. These Tdp1-DNA adducts can only be removed by wild-type Tdp1 (Figure 2) (Interthal et al., 2005b). This finding suggests that SCAN1 might arise, at least in part, from accumulation of the Tdp1-DNA adducts and the inability of the cell to remove Tdp1^{H493R} in a timely manner (Dexheimer et al., 2008; Hirano et al., 2007).

Currently, the molecular basis of SCAN1 and the reason that mice deficient for Tdp1 do not develop ataxia are incompletely understood. Although there are no prominent tissue differences in gene expression nor evidence of positive selection of the Tdp1 protein (as reported in the Selectome database) between human and mouse (Proux et al., 2009), two observations suggest possible explanations for SCAN1 pathogenesis and the lack of ataxia in Tdp1-deficient mice. First, human Tdp1 is predominantly expressed in the cytoplasm of the neurons predicted to be affected in SCAN1, whereas mouse Tdp1 is predominantly expressed in the nucleus of the analogous neurons. Second, *in vitro* and cell culture experiments show that the p.His493Arg Tdp1 forms long lived Tdp1-DNA adducts (Hirano et al., 2007; Interthal et al., 2005b); therefore, development of SCAN1 may be dependent on this “mutagenic” property of p.His493Arg Tdp1.

5.1 Mitochondrial dysfunction model

The prominent cytoplasmic expression of Tdp1 in human Purkinje, dentate nucleus, anterior horn, and dorsal ganglion neurons suggests a cytoplasmic function for Tdp1. Given the mitochondrial localization of cytoplasmic Tdp1, this suggests 1) that the majority of Tdp1 in these neurons functions in the mitochondria and 2) that SCAN1 may be arising from mitochondrial dysfunction secondary to loss of mtDNA integrity. In contrast, the low expression of Tdp1 in the cytoplasm of these neurons in mice would suggest that Tdp1 plays a minor role in maintenance of the mouse mitochondrial genome or that the analogous neurons have less mtDNA damage in mice than in humans.

The human cerebellum contains post-mitotic neurons with a large mitochondrial population. Despite the non-proliferative nature of cerebellar neurons, the biogenesis of mitochondria and the maintenance of mitochondrial integrity are of central importance for survival of these neurons (Chen and Chan, 2009). The closed circular mitochondrial genome predisposes it to helical tension during mitochondrial replication, which is resolved by mtTopo I. In the nucleus, binding of Topo I to 8-oxoG rearranges the active site of Topo I and stabilizes it in an inactive conformation (Leshner et al., 2002). If the same occurs in mitochondria with mtTopo I, which encounters a much higher level of 8-oxoG, then Tdp1

will be critical for resolution of these lesions in mtDNA. Hypothetically, a repair process analogous to that in the nucleus would resolve these long-lived complexes: 1) protease cleavage of mtTopo I, 2) Tdp1 mediated cleavage and release of the mtTopo I peptide to leave an 8-oxoG 5' overhang and a 3'-phosphate, and 3) SP-BER. SP-BER would proceed by PNKP removal of the 3'-phosphate and OGG1 removal of the 5' 8-oxoG lesion, followed by mitochondrial polymerase- γ filling in the missing nucleotides and Lig3a ligating the DNA strand (Figure 4a).

Based on these observations, we hypothesize that the processing of trapped or long-lived mtTopo I-DNA intermediates is hindered in cells from SCAN1 patients by the reduced catalytic activity of p.His493Arg Tdp1. Additionally, we hypothesize that mitochondria lack DNA repair pathways redundant for the activity of Tdp1 since 3' end processing flap endonucleases that could resolve mtTopo I-DNA adducts have not been detected in mitochondria (Liu et al., 2002). In this model, trapped or long-lived mtTopo I-DNA intermediates interfere with mitochondrial transcription and contribute to mtDNA damage. In turn, both transcriptional dysfunction and genomic instability cause mitochondrial dysfunction and thereby poor cellular health. Relative to other brain neurons, cerebellar neurons may be highly sensitive to this mitochondrial damage since they have a lower tolerance for mitochondrial dysfunction (Chen et al., 2007; Hakonen et al., 2008) (Figure 4b).

In summary, therefore, the dysfunction of mitochondrial Tdp1 may contribute to the pathogenesis of SCAN1. Also, the absence of ataxia in Tdp1 deficient mice may arise because mouse cerebellar and spinal cord neurons have a lower requirement for Tdp1 processing of damaged mtDNA (Hirano et al., 2007).

5.2 Tdp1 neomorph model

The formation and accumulation of Tdp1-DNA adducts by the mutant p.His493Arg Tdp1 causes increased DNA breaks in cells expressing this mutant Tdp1 (Hirano et al., 2007) and thus suggests that p.His493Arg Tdp1 acts as a mutagen. *In vitro*, wild type Tdp1 is the only identified enzyme that can remove the mutant Tdp1 from the DNA (Interthal et al., 2005a). However, *in vivo* it is possible that nuclear Tdp1-DNA adducts are processed by a DNA repair mechanism such as HR that is present in proliferating unaffected cells but not in affected quiescent neurons. Alternatively, there may not be an alternative repair pathway but simply replacement of cells that die from accumulated Tdp1-DNA adducts in proliferating tissues and a failure of replacement for non-proliferating neurons.

As an extension of this hypothesis, one might consider that both mitochondrial dysfunction and the neomorphic properties of p.His493Arg Tdp1 contribute to the pathogenesis of SCAN1. The repair of damaged DNA is costly, and if the costs exceed cellular energy resources (ATP/NADH), then cell death results (Zong and Thompson, 2006). In this context, a mechanism that could lead to cell death is the depletion of NAD⁺ and ATP reserves by the over-activation of PARP1 due to accumulating SSBs created by Tdp1^{His493Arg}-DNA adducts in the nucleus and mitochondria. In the context of compromised mitochondria, such depletion of cellular energy reserves, which triggers permeabilization of the outer mitochondrial membrane and the release of cytochrome c and apoptosis-inducing factor

(AIF) (Wang et al., 2009), would occur at a lower threshold in affected versus unaffected cells of SCAN1 patients (Wang et al., 2011) (Chen and Chan, 2009). In this model, the neurons with the least energy reserves would be most sensitive and, unlike proliferating cells, difficult to replace (Figure 4c).

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Fig. 4. A and B.

Fig. 4. Models for the pathobiology of SCAN1. (A) Putative Tdp1 function in the mitochondria. Wild type Tdp1 removes the residual peptide from stalled mtTopo I complexes. Interfering DNA lesions are processed by OGG1 and by PNKP or APE1. Religation synthesis would then proceed by mitochondrial short patch-BER. (B) The mitochondrial dysfunction model. In SCAN1, p.His493Arg Tdp1 (in bold) removes peptides derived from Topo I-DNA complexes at a severely compromised rate. This sluggish repair leads to a higher steady-state level of mtDNA SSBs and DSBs. To bypass the lack of Tdp1, error-prone repair may generate mtDNA deletions which impair mitochondrial function leading to cell death and SCAN1. (C) The Tdp1 neomorph model. Mutagenic p.His493Arg Tdp1 is trapped on DNA, and since wild type Tdp1 most efficiently repairs p.His493Arg Tdp1-DNA adducts, the unresolved p.His493Arg Tdp1-DNA adducts in cells from SCAN1 patients will lead to much higher steady state levels of nuclear and mitochondrial DNA SSBs. This could cause neuron death both by SSB-induced programmed cell death and by cellular energy depletion secondary to mitochondrial dysfunction. The energy depletion would be accentuated by the increased energy requirement for DNA repair as exemplified by PARP1 mediated poly ADP-ribosylation. X = interfering lesion.

6. Future directions

The discovery of Tdp1 in mitochondria places the pathobiology of SCAN1 in a new light although whether specific mitochondrial pathology is relevant to the pathogenesis of SCAN1 remains to be elucidated. To that end, the generation of Tdp1^{His493Arg} mice will enable a thorough investigation of the physical and molecular characteristics of SCAN1.

Equally important is the precise elucidation of Tdp1 function in DNA processing. Research in mice and yeast has deciphered much about Tdp1 function but much remains to be discovered. Tdp1 orthologues have been described in 29 organisms, most recently in the plants *Arabidopsis sp.* and *Medicago sp.*, where Tdp1 repair of Topo I-induced damage is consistent with its role in mammalian cells (Lee et al., 2010; Macovei et al., 2010). As the time and cost of DNA sequencing continues to decline and techniques for probing the genome become more accessible to biologists, the study of emerging model organisms will provide valuable insights into the evolutionary conservation of Tdp1. This approach would allow more detailed evaluation of Tdp1 from an evolutionary perspective and enhance our mechanistic understanding. For example, this might enlighten us as to why the *Drosophila melanogaster* homologue *glaiKit* appears to have a function distinct from that of the mammalian and plant Tdp1 homologues (Dunlop et al., 2000; Dunlop et al., 2004).

The study of SCAN1 has also defined Tdp1 as a reasonable drug target for other diseases. The absence of neurological disease in Tdp1 deficient mice and the adolescent onset of SCAN1 in humans suggest that Tdp1 could be inhibited briefly without severe adverse consequences. Since Tdp1 increases resistance to the Topo I poisons used as anticancer agents, these findings suggest that a combination therapy of Topo I poisons with Tdp1 inhibitors might enhance the efficacy of the Topo I poisons as anticancer drugs (Marchand et al., 2009).

7. Conclusion

Mitochondrial dysfunction is not yet the *sine qua non* of SCAs, but it is increasingly reported in neurodegenerative diseases. Besides the SCAs, mitochondrial dysfunction has been reported as contributing to the pathobiology of aging, Alzheimer disease, Parkinson disease, Huntington disease and amyotrophic lateral sclerosis. Much of this work has focused on mitochondrial-derived reactive oxygen species; however, the contribution of mitochondrial fusion and fission to neuronal health and disease as well as other mitochondrial processes remain to be explored (Lin and Beal, 2006; Westermann, 2010). SCAN1 is emblematic of the interplay between the nuclear and mitochondrial genomes and how dysfunction in both organelles can jointly contribute to disease. This dual nuclear and mitochondrial pathobiology will need to be taken into consideration in experimental design as well as in the classification and clinical management of neurologic disorders.

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