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Broken strands, broken minds: Exploring the nexus of DNA damage and neurodegeneration

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ABSTRACT

Neurodegenerative disorders are primarily characterized by neuron loss progressively leading to cognitive decline and the manifestation of incurable and debilitating conditions, such as Alzheimer's, Parkinson's, and Huntington's diseases. Loss of genome maintenance causally contributes to age-related neurodegeneration, as exemplified by the premature appearance of neurodegenerative features in a growing family of human syndromes and mice harbouring inborn defects in DNA repair. Here, we discuss the relevance of persistent DNA damage, key DNA repair mechanisms and compromised genome integrity in age-related neurodegeneration highlighting the significance of investigating these connections to pave the way for the development of rationalized intervention strategies aimed at delaying the onset of neurodegenerative disorders and promoting healthy aging.

Abbreviations: 8-oxoG, 8-oxo-7,8-dihydroguanine; AD, Alzheimer's disease; AIM2, Absent In Melanoma 2; ALS, Amyotrophic Lateral Sclerosis; Alt-NHEJ, Alternative non-homologous end joining; AOA1, Ataxia with Oculomotor Apraxia; APE1, AP-endonuclease; Aptx, Aprataxin; AT, Ataxia-telangiectasia; ATAC-seq, assay for transposase-accessible chromatin with sequencing; ATLD, Ataxia telangiectasia-like disorder; ATM, ataxia-telangiectasia mutated; ATP, Adenosine triphosphate; BER, Base Excision Repair; BRAC1, Breast Cancer gene 1; C9orf72, chromosome 9 open reading frame 72; CGAMP, cyclic GMP-AMP; CGAS, Cyclic GMP-AMP synthase; CNS, central nervous systems; COFS, Cerebro-oculo-facioskeletal syndrome; CS, Cockayne Syndrome; CSA, Cockayne syndrome group A; CSB, Cockayne syndrome group B; DDB1, DNA damage-binding protein 1; DDB2, DNA damage-binding protein 2; DDR, DNA damage response; DNA–PK, DNA-dependent protein kinase; DSB, DNA double strand break; DsDNA, double-strand DNA; ERCC1, excision repair cross complementation group 1; FEN1, Flap Endonuclease 1; Fus, Fused in sarcoma; GG-NER, Global Genome-Nucleotide Excision Repair; HR, Homologous Recombination; HD, Huntington's disease; IBs, inclusion bodies; ICAM-1, intercellular adhesion molecule; Ikβ, inhibitor of nuclear factor kappa B; IL-1R, Interleukine 1 receptor; IL-6R, Interleukine 6 receptor; IRF3, interferon regulatory factor 3; JAK, Janus Kinase; LIG3, ligase 3; *Lig4*, *Ligase 4*; LTD, long-term depression; LTP, long-term potentiation; MCPH1, Primary microcephaly 1; MRE11, meiotic recombination 11 homolog 1; MRN complex, MRE11-RAD50-NBS1 complex; MS, Multiple Sclerosis; NAD^+, Nicotinamide adenine dinucleotide; NBS, Nijmegen breakage syndrome; NDDs, Neurodegenerative diseases; NEMO, NF-κB essential modulator; NER, nucleotide excision repair; NF-κB, Nuclear Factor kappa B; NHEJ, non-homologous end joining; NLRP3, NLR family pyrin domain containing 3; PARP1, Poly [ADP-ribose] polymerase 1; PARylation, poly-ADP-ribosylation; PD, Parkinson's disease; PGC1a, Peroxisome proliferator-activated receptor-gamma coactivator PGC-1alpha; PNS, Peripheral Nervous Systems; POL δ/ε, polymerase δ/ε; POLθ, Polymerase θ; RAD51, RADiation sensitive protein 51; RAG1, recombination-activating gene 1; RAP80, receptor-associated protein 80; RIG1, Retinoic Acid Inducible Gene-1; RIPK1, Receptor-interacting serine/threonine-protein kinase 1; RLRC, R-loop resolution complex; RNAPII, RNA polymerase II; ROS, reactive oxygen species; RPA, Replication Protein A; SASP, Senescence-associated secretory phenotype; SCAN1, Spinocerebellar Ataxia with Axonal Neuropathy Type1; SETX, Senataxin; SIRT1, silent information regulator sirtuin 1; SMA, Spinal Muscular Atrophy; SMN, Survival Motor Neuron; SSA, single-strand annealing; SSB, Single Strand Break; STING, Stimulator of interferon IFN genes; TBK1, TANK-binding kinase 1; TC-NER, Transcription-coupled Nucleotide Excision Repair; Tdp1, Tyrosyl-DNA Phosphodiesterase 1; Tet, Ten-eleven translocation; Tet3, Ten-eleven translocation 3; TFIIH, Transcription factor II H; TLR, Toll-like receptor; TLR4, Toll-like receptor 4; TLR9, Toll-like receptor 9; TNFα, Tumor Necrosis Factor α; Top1, topoisomerase 1; Top1ccs, topoisomerase 1 cleavage complexes; Top2ccs, topoisomerase 2 cleavage complexes; TTD, Trichothiodystrophy; TTDA, trichothiodystrophy group A; UCP2, uncoupling protein-2; UPS, ubiquitin-proteasome system; UV–DDB, UV-damaged DNA binding protein; UVsS, UV sensitive syndrome; UVSSA, UV stimulated scaffold protein A; XAB2, Xeroderma pigmentosum group A XPA-binding protein 2; XP, Xeroderma Pigmentosum; XLF, X-Ray Repair Cross Complementing 4 XRCC4-like factor; XPA, Xeroderma Pigmentosa Group A; XPB, Xeroderma Pigmentosa Group B; XPC, Xeroderma Pigmentosa Group C; XPD, Xeroderma Pigmentosa Group D; XPF, Xeroderma Pigmentosa Group F; XPG, Xeroderma Pigmentosa Group G; XRCC1, X-Ray Repair Cross Complementing 1; XRCC4, X-Ray Repair Cross Complementing 4; ZPR1, zinc finger protein 1.

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1. Introduction

Neurodegenerative diseases (NDDs) are recognized as the second most prevalent cause of morbidity and disability worldwide, after cardiovascular diseases[1]. The hallmark of these widespread NDDs, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and multiple sclerosis (MS)[2], is the gradual erosion of neuronal function in both the peripheral and central nervous systems (PNS; CNS)[2]. The prevalence of AD, PD, HD and ALS increases significantly and steadily with ageing [3]. Beyond the classic NDDs, a fascinating spectrum emerges, linking neuronal loss to DNA repair-deficient syndromes such as Ataxia telangiectasia, Nijmegen breakage syndrome, Spinocerebellar ataxia, Triple-A syndrome, Cockayne syndrome, and Xeroderma Pigmentosum syndrome. In these syndromes, faulty DNA repair mechanisms result in the accumulation of diverse DNA lesions across various cell types,

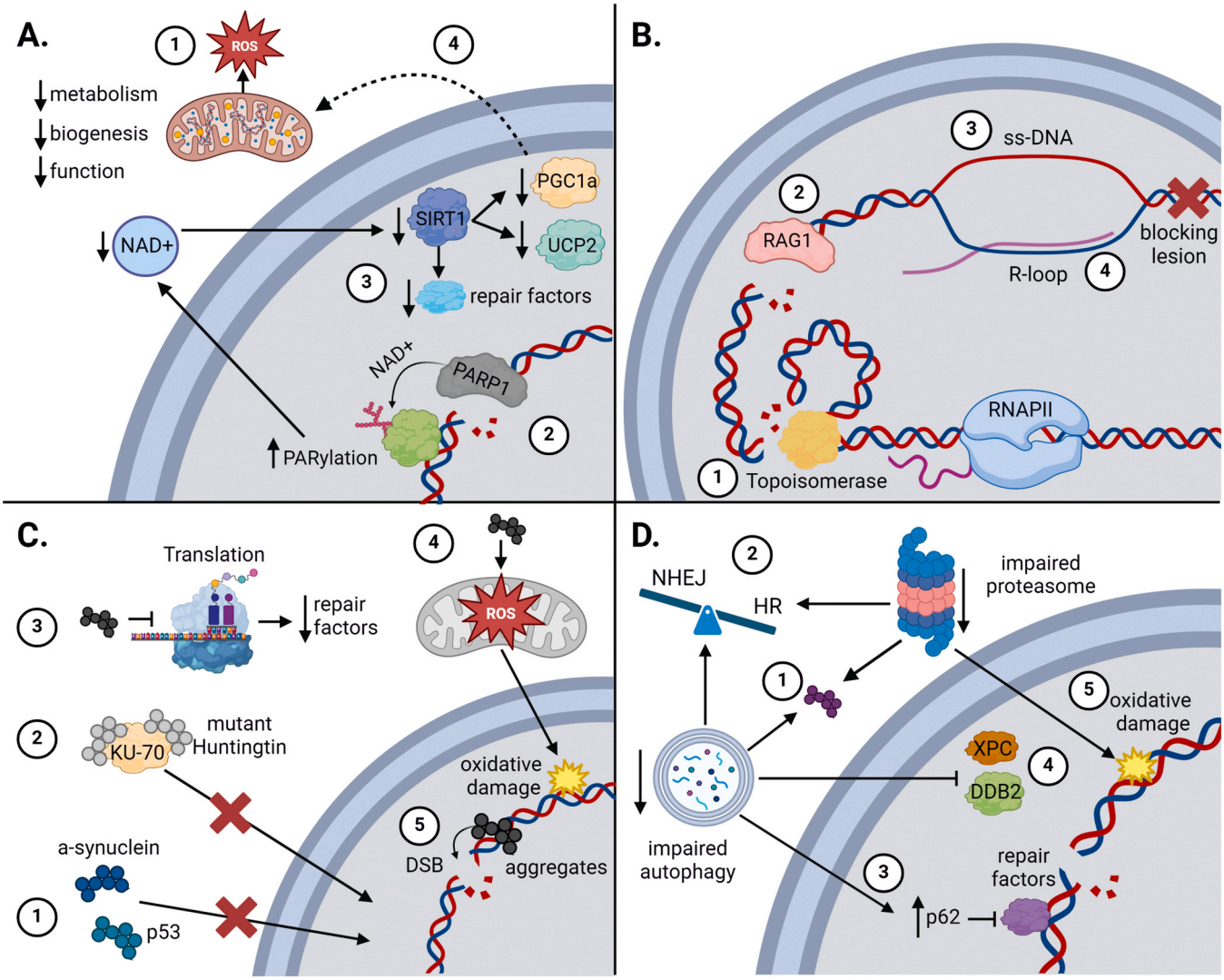

Fig. 1. Sources of intrinsic genome instability in neurons. (A) Mitochondria dysfunction leads to genome instability and vice versa. Dysfunctional mitochondria contribute to genome instability through the release of reactive oxygen species (ROS) (1). Conversely, DNA damage triggers the activation of PARP1, which catalyzes PARylation using NAD^+ (2). Excessive DNA damage leads to hyperactivation of PARP1, depleting the NAD^+ pool. The diminished NAD^+ pool disrupts the function of SIRT1. Impaired SIRT1 function affects various repair factors, thereby exacerbating genome instability (3). Additionally, SIRT1 influences the roles of PGC1a and UCP2, which regulate mitochondrial function (4). (B) Transcription poses a threat for genome stability, when transcriptional levels are elevated and/or when the repair machinery is compromised. Unrepaired single or double-strand breaks can form due to various transcription-related processes. This includes the resolution of transcription-induced supercoiled structures by topoisomerases (1) or due to transcriptional rewiring-mediated activation of RAG1 recombinase (2). Conversely, blocking transcription can also contribute to genome instability. This occurs through exposure of single-stranded DNA, which is susceptible to genotoxic agents (3). Additionally, the formation of R-loops can occur, further contributing to genome instability (4). (C) Protein aggregation has a reciprocal interaction with genome stability. Repair factors (e.g a-synuclein) as well as DDR-related proteins (e.g p53) can themselves form aggregates and interfere with the repair of DNA lesions (1). In other cases, pathological aggregates (e.g mutant huntingtin, amyloid beta) bind to repair factors (KU-70, MRE11, BRAC1) and trap them in the cytoplasm, preventing their translocation to the nucleus (2). Additionally, aggregates disrupt translation leading to a decrease in the availability of repair factors (3). Protein aggregates can also perturb mitochondrial function, resulting in the production of reactive oxygen species (ROS) that cause oxidative DNA damage (4). Aggregates can finally directly cause DSBs by binding to the DNA helix (5). (D) Impaired proteostasis (autophagy and proteasome) contributes to intrinsic DNA damage. Reduced efficiency of proteostasis fails to remove protein aggregates linked to genome instability (1). This dysfunction also favors non-homologous end joining (NHEJ), an error-prone DNA repair pathway, over homologous recombination (HR) (2). Decreased autophagic flux leads to nuclear accumulation of p62, which inhibits the binding of repair factors such as BRCA1, RAD51, and RAP80 (3). Additionally, downregulation of autophagy compromises the nucleotide excision repair (NER) pathway by affecting two NER repair factors, XPC and DDB2 (4). Dysfunctional proteasomes have finally been linked to the induction of oxidative DNA lesions, directly contributing to genome instability (5). Figure was created with Biorender.com.

including glial cells, instigating premature age-related neurodegeneration. The premature onset of age-related neurodegeneration in patients with genome maintenance defects unequivocally underscores the role of accumulating irreparable DNA lesions as the causal pathway leading to NDDs. The neurodegenerative features observed in syndromes associated with inborn defects in DNA repair are heterogeneous and vary in terms of severity or onset [4]. This diversity likely stems from differences in the type and genomic location of the DNA lesions, the involvement of different (non)-neuronal populations, variations in the transcriptional activity between cells in distinct neuronal populations and from the function of certain DNA repair proteins in multiple DNA repair mechanisms or DNA-templated mechanisms outside the canonical DDR [5–7]. Here we aim to unveil a nuanced perspective into the intricate and multifaceted role of genome instability as a pivotal and causative contributor to the complex landscape of neurodegeneration.

2. Sources of genome instability leading to age-related neuronal decline

Neurons, known for their high energy demands, face significant consequences when mitochondrial function alters, primarily manifesting as a disruption in ATP production. Diminished ATP levels compromise the ability of neurons to meet their energy requirements. Additionally, mitochondrial dysregulation triggers the generation of cytoplasmic reactive oxygen species (ROS), contributing to oxidative DNA damage (Fig. 1A) by incorporating 8-oxo-7,8-dihydroguanine (8-oxoG) into DNA [8]. The presence of 8-oxoG can dysregulate gene transcription and its erroneous repair results in mutagenesis, a major contributor to aging and disease. Conversely, the relationship between DNA damage and mitochondrial homeostasis is reciprocal, particularly through the involvement of NAD^+. NAD^+ serves as a common substrate for two enzymes, PARP1 and SIRT1. At times of excessive DNA damage or in case of defective DNA repair, an overstimulation of PARP1 is observed, impacting the NAD^+ reservoir [9]. PARP1, recruited to various DNA lesions, catalyzes poly-ADP-ribosylation (PARylation), adding multiple ADP-ribose units to DNA-interacting proteins and DNA repair factors. PARylation acts as a signal for DNA repair-related proteins, inducing chromatin decondensation at damaged sites [10]. Depletion of NAD^+ directly affects mitochondria, primarily due to the impaired function of SIRT1. This disruption leads to the dysregulation of PGC1a, a master regulator of mitochondrial biogenesis and function, as well as diminished expression of UCP2, a key regulator of metabolism and mitochondrial ROS [11,12]. Additionally, SIRT1 plays a role in DNA repair by modulating the function of various repair factors [13,14]. In neurons characterized by a high energetic profile, the consequences of PARP1 hyperactivation are particularly detrimental. Notably, genetic deletion of PARP1 or exogenous supplementation of NAD^+ results in alleviation of mitochondrial dysfunction [15]. Mitochondrial deregulation is also a hallmark of aging, where persistent damage signals to PARP1, leading to a reduction in NAD^+ and subsequent mitochondrial impairment during the aging process [15]. This intricate interplay between mitochondrial dysfunction and DNA damage underscores the complex web of factors contributing to neuronal health and degeneration.

Transcription is vital for normal cellular function. However, it can also contribute to genomic instability (Fig. 1B), particularly in highly transcribing, post-mitotic neurons [16–18]. In line, genomic loci with increased transcriptional activity experience a substantial amount of mutagenesis and recombination [19,20]. The process of mRNA synthesis works by unwinding the DNA structure, facilitating chromatin remodeling. The negative supercoiling induced by RNAPII creates unstable regions of single-strand DNA that are prone to breakage or chemical interactions, ultimately resulting in DNA damage. Transcription also contributes to the formation of non-B DNA structures, such as R-loops, whose levels increase when RNAPII is blocked, *e.g.,* in the presence of transcription-blocking DNA lesions affecting gene expression programs while threatening genomic integrity [21]. So far, neuronal DNA damage has not been attributed to unresolved R-loops. Intriguingly however, in genomic regions such as nucleotide repeats, which are often expanded in neurodegenerative diseases, R-loops are formed more frequently and are more difficult to resolve [22,23]. Moreover, in Spinal Muscular Atrophy (SMA), neurodegeneration specifically in spinal motor neurons is caused by the downregulation of critical factors that are components of the R-loop resolution complex (RLRC), such as SETX, SMN, and ZPR1 [24]. It remains to be seen to what extent R-loops can act independently as a source of neurodegeneration or whether they represent a side product of DNA damage.

Genome maintenance pathways are physiologically linked with transcriptional rewiring of neurons required for modulation of neuronal activity, which is considered the foundation of learning and memory, and its decline is connected to the cognitive defects of neurodegenerative diseases. Neuronal plasticity classified to short term and long term potentiation (LTP) and depression (LTD) refers to the ability of neurons to modify the strength and efficiency of synaptic transmission to pre-existing synapses [25]. BER oxidizes 5-methylcytosine to initiate active DNA demethylation through the Tet family proteins. Tet3 signaling drives synaptic plasticity by regulating gene expression in response to global synaptic activity changes [26,27]. LTP and LTD are also tightly associated with the controlled introduction and repair of DNA double strand breaks (DSBs) in genes controlling synaptic activity [26,28]. In support, mice subjected to context fear conditioning present with an increased expression of RAG1, a protein mediating the rearrangement and recombination of genes by generating DSBs and activating DNA ligases and DNA repair proteins for re-joining the new gene segments [26,29]. Neuronal plasticity-mediated transcriptional activity also coincides with the recruitment of topoisomerase cleavage complexes to resolve topological constrains [16]. Top1 and Top2ccs though can induce SSBs or/and DSBs, when not faithfully re-ligated.

Transcriptional stress and transcription-mediated DSBs and SSBs are thus intrinsically relevant to neuron physiology. Nevertheless, one can assume that in cases where the efficiency of DNA repair pathways declines, as in ageing, the accumulation of neuronal DNA damage can occur, leading to neurodegenerative phenotypes. In this context, it is interesting that oxidative DNA damage can lead to the accumulation of Top1ccs [30], rendering neurons even more vulnerable to this kind of lesion.

Due to their polarization, neurons have unique requirements regarding their proteostatic mechanisms compared to other cell types [31]. As a result, dysregulation of protein homeostasis due to mutations, intrinsically weaker proteostatic mechanisms or extreme stress, renders neurons more vulnerable to accumulation of protein aggregates. These aggregates ultimately cluster to create insoluble structures named inclusion bodies (IBs) [32–34]. Protein aggregates are known to contribute heavily to the neurodegenerative phenotype [35], and, intriguingly so, are known to promote genomic instability (Fig. 1C). *In vitro* assays indicate that recombinant α-synuclein and amyloid-β fibrils, the major protein aggregates related to AD and PD respectively, as well as aggregation-prone luciferase, often generate DNA breaks [36,37]. Moreover, pathological aggregates in neurons directly bind to DNA and cause DSBs [38,39]. Interestingly, in some cases the neurotoxic aggregates are themselves repair factors or proteins involved in DDR. This is the case with aggregation of cytoplasmic a-synuclein, which limits the nuclear levels of the protein and reduces the efficiency of DSB repair, since a-synuclein is additionally involved in the repair process [40]. Protein aggregates may also indirectly affect the levels of DNA repair proteins by interfering with the protein translation machinery [41] or trigger the cytoplasmic sequestration of proteins involved in DNA repair. Mutant Huntingtin interacts with Ku70 and functionally impairs Ku70-dependent DNA-dependent protein kinase (DNA–PK) activity for NHEJ of DSBs *in vitro* and *in vivo*, leading to the accumulation of DNA damage in neurons [42]. In AD, accumulation of amyloid beta is linked to reduction of BRAC1 and MRE11[43]. In AD models p53 forms fibrils

and upon induction of DNA damage is mislocalized, thus leading to impaired DDR [44]. Finally, aggregates can also indirectly contribute to genome instability through the generation of ROS, leading to oxidative stress [45]. Protein aggregates can also be caused by impairment of proteostatic mechanisms, i.e., autophagy and the ubiquitin-proteasome system (UPS) (Fig. 1D). Autophagy inactivation leads to an XPC, DDB2-mediated NER deficiency [46]. Compromised autophagy also results in an increase in nuclear localization of p62, which prevents the binding of distinct DNA repair proteins involved in DSB repair, such as BRCA1, RAD51 and RAP80 [47]. Impairment of autophagy and UPS also swifts the preference from the error proof homologous recombination (HR) pathway to the error prone NHEJ [48,49]. Inhibition of the proteasome in rat neurons leads to increased oxidative DNA damage levels [50]. Different DNA repair factors were shown to interact with the proteasome [51–53]. This interaction in some cases is essential for their recruitment on DNA lesions [51], thus opening the question whether proteasome deficiency could also affect genome maintenance through this pathway. The unique physiological requirements of neuron physiology, including excess energy demands, neuronal plasticity-mediated transcriptional rewiring, and high rates of protein turnover, have a significant impact on genome stability and vice versa. Under normal conditions, neuronal cells can cope with these demands and maintain their genome integrity. However, an imbalance in either aspect of neuron physiology, such as mitochondrial dysfunction, decline of proteostatic or DNA repair mechanisms, or the presence of transcription-blocking lesions, leads to a vicious cycle between genome instability and the decline of neuronal function. Ultimately, this cascade results in neurodegeneration.

3. Linking genome maintenance defects to neurodegeneration

When oxidative DNA lesions, transcription-blocking DNA insults or DNA breaks are inflicted on the neuronal genome, the double helix must be repaired and preserved throughout the entire lifetime of the cell. To meet this challenge, cells have evolved machineries to counteract structural DNA modifications (e.g., nicks, gaps, DSBs), and the myriad alterations that may threaten cell viability (Table 1). BER is the main pathway dedicated to removing one of the most well-characterized oxidative lesions, 8-oxoG [54,55]. The BER-mediated repairing process involves lesion recognition and excision by a DNA glycosylase, forming an intermediate abasic site. Incision of the resulting abasic site by an AP-endonuclease (APE1) or AP-lyase action generates a Single

Table 1
Defective DNA repair mechanisms and associated syndromes with pronounced neurodegeneration.

Type of DNA damage	Repair Pathway	Affected Proteins	Disease	Characteristics
Bulky lesions	Global Genome Nucleotide Excision Repair (GG-NER)	XPA-XPG	Xeroderma Pigmentosum (XP)	• Skin cancer • Hyperreflexia • Mental retardation • Sensorineural deafness • Spasticity • Seizures
	Transcription Coupled Nucleotide Excision Repair (TC-NER)	CSA, CSB, UVSSA, XPB, XPD, XPF, TTDA, XPG	Cockayne Syndrome (CS)	• Accelerated aging • Neurodevelopmental defects • Growth defects • Cachexia • Microcephaly • Retinal degeneration
		XPB, XPD	Trichothiodystrophy (TTD)	• Accelerated aging • Developmental abnormalities • Neurodegeneration • Photosensitivity • Ichthyosis • Short, brittle hair
8-oxo-7,8-dihydroguanine (8-oxoG)	Base Excision Repair (BER)	Embryonic Lethality	Embryonic Lethality	-
Single Strand Breaks (SSBs)	Single Strand Breaks Repair	TDP1	Spinocerebellar Ataxia with axonal neuropathy Type1 (SCAN1)	• Cerebellar ataxia • Sensorimotor axonal neuropathy • Dysarthria • Loss of pain, touch and vibration sensation
		Aprataxin	Ataxia with oculomotor apraxia (AOA1)	• Ataxia • Oculomotor apraxia • Neuropathy • Cerebellar atrophy • Dysarthria
Double Strand Breaks (DSBs)	Homologous Recombination (HR)	ATM	Ataxia telangiectasia (A-T)	• Ataxia • Cerebellar atrophy • Immunodeficiency • Susceptibility to cancer
		MRE11	Ataxia telangiectasia-like disorder (ATLD)	• Ataxia
	Non-Homologous End Joining (NHEJ)	Nibrilin	Nijmegen Syndrome (NBS)	• Microcephaly • Immunodeficiency • Cancer predisposition
		Microcephalin	Primary Microcephaly 1 (MCPH1)	• Microcephaly
		Ligase 4	Ligase 4 Syndrome (LIG4)	• Microcephaly • Immunodeficiency • Developmental delay

The table shows the different DNA lesions (8-oxoG, DSB, SSB, bulky lesions) and the respective DNA repair (sub)pathways (BER, HR, NHEJ, TOP1, GG-NER, TC-NER). With the exception of 8-oxoG, each type of DNA damage is linked to a variety of DNA repair syndromes that carry inborn mutations in distinct DNA repair genes and manifest with neurodegeneration. Also, the table presents the symptoms of each DNA repair related syndrome.

Strand Break (SSB). The resulting lesion is repaired by SSB-repair pathway, that involves either gap filling by a DNA polymerase or incision of a larger stretch of DNA (2-13 nucleotides) by flap endonuclease 1 (FEN1) and replacement by polymerase δ/ε (POL δ/ε). DNA ligase seals the nick and restores the lesion [56–58]. SSBs can also be generated by TOP1 DNA cleavage complexes (Top1cc). TOP1-activity relaxes supercoiled DNA. When Top1-mediated lesions persist, they lead to SSBs [59]. Assessing the effect of defective BER on neurodegeneration in mammals is cumbersome, since the great majority of mutations in BER genes lead to embryonic lethality. Yet, the significance of SSB repair defects in the premature onset of neurodegenerative features is evident in two SSB repair syndromes, namely spinocerebellar ataxia with axonal neuropathy Type1 (SCAN1) and ataxia with oculomotor apraxia (AOA1). SCAN1 is caused by mutations in *Tyrosyl-DNA Phosphodiesterase 1* (*Tdp1*) gene, whereas AOA1 by mutations in *Aprataxin* (*Aptx*) gene. TDP1 is responsible for resolving Top1ccs, whereas APRATAXIN deadenylates 5'DNA ends resulting from oxidative lesions that cannot be further processed by LIGASE IV/XRCC1 complex [60]. These genetic diseases are primarily defined by nervous system deficits such as ataxia, neuropathy, and cerebellar atrophy and dysarthria [59,61,62]. As the disease progresses, patients with SCAN1 also experience impaired sensations of pain, touch, and vibration [63].The neuronal specificity of AOA1 and SCAN1 indicate the importance of SSBs in the development of neurodegeneration.

For bulky helix-distorting damage, the principal repair mechanism is the evolutionarily conserved nucleotide excision repair (NER). NER recognizes and removes helical distortions throughout the genome (i.e., global genome repair; GG-NER), or selectively from the actively transcribed part of the genome (i.e., transcription-coupled repair; TC-NER) [64,65]. In GG-NER, the lesion is recognized by the UV–DDB complex composed of DDB1 and DDB2. In TC-NER, DNA damage is sensed because the elongating RNAPII is blocked at damaged DNA sites on the actively transcribed strand of genes. RNAPII then recruits the DNA-dependent ATPases CSB and CSA, whose binding likely helps to backtrack RNAPII allowing the remaining NER factors to access the DNA lesion. Following damage recognition by the GG- or TC-NER sub-pathways, TFIIH and XPA are recruited to the DNA damage site and together with RPA that binds the ssDNA opposite the DNA lesion, they stabilize the damaged DNA for incision. ssDNA binding activates endonucleases ERCC1–XPF and XPG that cleave the 5′ and 3′ side of the 24–32nt bulky adduct. Removal of the lesion is followed by the polymerase activity of the DNA replication machinery that fills in the single-stranded DNA gap and the new DNA fragment is then sealed by DNA ligase I or IIIα-XRCC1 complex [65]. In humans, inborn mutations in NER genes are associated with syndromes that are both heterogeneous and pleiotropic [66]. Defects in GG-NER give rise to the skin cancer-prone disorder xeroderma pigmentosum (XP; affected proteins: XPA through XPG). Defects in TC-NER lead to a heterogeneous group of progeroid (accelerated ageing) disorders that are phenotypically distinct from XP, including the Cockayne syndrome (CS; affected proteins: CSA, CSB, UVSSA, XPB, XPD, XPF and TTDA and certain mutations in the gene encoding XPG) and Trichothiodystrophy (TTD; affected proteins: XPB, XPD, P8) [67–70]. Although XP, CS, and TTD are derived from mutations in genes involved in the same DNA repair mechanism or even in the same NER gene [71], their clinical outcome is remarkably diverse. The clinical phenotype of TTD includes developmental abnormalities, neurodegeneration, photosensitivity, ichthyosis and short, brittle hair, often characterized by reduced cysteine content [72]. Neurological abnormalities in TTD patients comprise microcephaly, mental impairment, ataxia and reduced levels of myelination [73]. In XP, the time of onset of neurological abnormalities varies dramatically from the age of two to middle age [74,75]. A smaller percentage i.e. <30 % of the patients with defects in XPA, XPB, XPD, or XPG manifest neurological deficits of varying severity, including isolated hyperreflexia, progressive mental retardation, sensorineural deafness, spasticity, or seizures [76]. In CS, patients suffer from progressive neurodevelopmental defects along with an early (at birth) or late (late childhood or even adulthood) onset of growth defects and cachexia, microcephaly, retinal degeneration, and a reported life expectancy of ~12 years. The CS pathological symptoms are more severe in the CS variant Cerebro-oculo-facioskeletal syndrome (COFS; life expectancy <2 years) or considerably milder in the UV sensitive syndrome (UVSS; affected proteins: CSB, CSA, UVSSA) where the stability of CSB is compromised [77–79]. Unlike CS patients, whose neuropathology is linked to myelin abnormalities, XP and TTD patients present with relatively unaffected neurons and axons [73]. CSB has also been implicated in adult neurogenesis. Loss of CSB is accompanied by impaired neurogenesis and differentiation of neuronal progenitors [80]. More recently, the NER factors XPF, XPG, XAB2 and CSB have been implicated in the resolution of R-loops [81]. It remains to be determined whether or to what extent their function related to R-loop processing is also linked to the onset of neurodegenerative diseases.

DSBs are highly cytotoxic lesions that if left unrepaired, may result in massive loss of genetic information, genomic rearrangements, or cell death. DSBs are repaired by non-homologous end joining (NHEJ) and homologous recombination (HR). NHEJ modifies the broken DNA ends, and ligates them together with little or no homology, generating deletions or insertions. In contrast, HR uses an undamaged DNA template on the sister chromatid or homologous chromosome to repair the break, leading to the reconstitution of the original sequence. HR only occurs during S-G2 phase and therefore is not active in post mitotic neurons. In contrast, NHEJ operates in all phases of the cell cycle and is inherently error-prone. In canonical NHEJ, DSBs are recognized by KU70/80 and DNA-PK and ligated with Ligase IV (LIG4), which is stabilized by X-Ray Repair Cross Complementing 4 (XRCC4), and XRCC4-like factor (XLF). Alternative NHEJ (alt-NHEJ) and single-strand annealing (SSA) involves end resection of the broken strands resulting in single-strand overhangs. End resection exposes short homologous sequences that are used as template by Polymerase θ (POLθ). The resulting DNA flaps are excised by NER structure specific endonuclease ERCC1-XPF and the newly synthesized DNA strands are ligated by LIG3 [82]. There is ample evidence that inborn defects in single- and double strand DNA repair associate with the premature onset of neurodegenerative features in man. Ataxia telangiectasia (A-T) is caused by mutations in ATM kinase. Patients with A-T present immune deficiency, increased cancer susceptibility and progressive cerebellar atrophy [83]. Similar phenotypes are exhibited by patients with mutations in *Mre11*, i.e. Ataxia telangiectasia-like disorder (ATLD)-[17,83]. MRE11 is a component of MRN complex, which recognizes the broken DNA ends and then rapidly recruits and activates ATM. Surprisingly, patients with mutations in different genes involved in DSB repair downstream from recognition and ATM activation, i.e. *Nbs1* (Nijmegen breakage syndrome-NBS), *Mcph1/Brit1* (Primary microcephaly 1-MCPH1), or *Lig4* (LIG4 syndrome) present with microcephaly rather than progressive cerebellar ataxia. In the case of A-T, it is suggested that a deficiency in ATM rather than a deficiency in other DSB repair-related proteins makes cells resistant to DNA damage-induced apoptosis. This resistance results in the accumulation of genomic instability in post-mitotic neurons, contributing to the progressive symptoms characteristic of ataxia.

The neuronal specificity of single-strand break repair-related syndromes highlights the sensitivity of neurons to oxidative lesions, likely due to their high metabolic demands and transcription-related DNA lesions from transcriptional rewiring. Unrepaired DNA lesions that hinder transcription could also be a cause of neurological deficits in nucleotide excision repair syndromes, especially considering the role of several proteins involved in resolving R-loops. Interestingly, ataxia-telangiectasia mouse models have shown an accumulation of topoisomerase I cleavage complexes in cerebellar cell populations due to reduced ubiquitin-mediated degradation of TDP1, stemming from a DNA repair-independent function of ATM. [84].

Moreover, ataxia is a common neurodegenerative phenotype in DNA-repair-related syndromes (see Table 1). It is observed in SSB repair neuron-specific syndromes, in NER syndromes like TTD, and in DSB repair syndromes such as A-T and ataxia with oculomotor apraxia

(AOA). The pronounced phenotype of ataxia could result from the heightened sensitivity of cerebellar cell populations to DNA damage, due to their unique physiology and high metabolic demands. Indeed, Purkinje cells of ATM knockout mice are more sensitive to DNA lesions. ATAC-seq in an A-T mouse model revealed that in contrast to cerebellar granule cells, Purkinje cells have open chromatin regions that in combination with genomic instability lead to R-loop formation driven disruption in gene expression, which ultimately results in cerebellar ataxia [85].

Besides DNA repair syndromes, NDDs further support the relevance of DNA damage to neurodegeneration. In familial ALS the role of DNA damage as the source of the disease onset is evident. Mutations in *Fus* and *Tdp43* directly link ALS onset with DNA damage due to the DNA repair role of FUS and TDP43, as well as to their interactions with NHEJ repair factors [86,87]. Motor neuron disease-associated loss of nuclear TDP-43 is linked to DNA double-strand break repair defects [86]. Mutations in the C9orf72 repeat expansion are known to form abnormal nuclei acid structures, such as hairpins, G-quadruplexes, and R-loops, which can also be the source of DNA damage [88]. In contrary, familial cases of AD and PD involve mutations of genes that contribute to aggregation and/or accumulation of Aβplaques and a-synuclein respectively [89,90]. Yet, in sporadic cases of NDDs numerous data suggest the importance of DNA damage in the phenotype of the diseases. Elevated levels of DNA strand breaks, a reduction in the levels of DSB repair proteins such as DNA-PKcs and MRN complex proteins, and decreased BER activity have been described in AD patients [91–93]. Oxidative lesions and SSBs have been reported in ALS cases, whereas mitochondrial DNA damage is reported in PD patients [94,95].

4. DNA damage-driven neuroinflammation

DNA damage and DNA repair-deficient syndromes have been linked with activated inflammatory responses [96–98]. Ablation of *Ercc1* in several cell types or tissues in mice models has shown inflammatory phenotypes [99–102]. Patients with AT syndrome also have a wide spectrum of immunological abnormalities regarding mainly the adoptive immune system [103]. Parallel studies suggest in many cases that neuroinflammation coincides with DNA damage. In NER, the abrogation of *Csa* or *Csb* and *Xpa* genes in double mutant mice ($Csb^{-/-}/Xpa^{-/-}$, $Csa^{-/-}/Xpa^{-/-}$) reliably mimics the neurodegenerative features seen in CS patients and shows an upregulation of inflammatory markers, such as ICAM-1, TNFα, p-p65, as well as the activation of glial cells in neuronal tissues [104]. Moreover, rats with a missense mutation in *Atm* show induction of type I interferon and neurodegeneration [105]. Neuroinflammation is also a critical risk factor for most of the neurodegenerative disorders, i.e. AD, PD, ALS and MS [106]. Microglia, the primary innate immune cells of the central nervous system, make up ~10 % of all brain cells, and may causally contribute to the onset of neurodegenerative features at the early stages of the disease process [107,108]. Consistently, drugs aimed at targeting some key molecules involved in inflammatory signaling pathways e.g., NLRP3 inflammasome, TLR/NF-κB/TNF-a signaling, IL-1R, IL-6R, JAK or RIPK1 and nonsteroidal anti-inflammatory drugs have been developed for AD, PD and ALS [109]. These treatments reduce neuroinflammation and rescue neurotoxicity to a significant extend indicating that aberrant immune responses are major contributors to phenotypes associated with NDDs. In many studies related to AD and PD, neuroinflammation is driven by the presence of aggregated amyloid plaques or a-synuclein respectively, which are sensed by Toll-like receptor 4 (TLR4) and subsequently activate nuclear factor κB (NF-κB) [110–114]. Yet, the inflammatory phenotypes of DNA repair syndromes and the tight relation of DNA damage to inflammation [96,98] has emerged the question of whether neuroinflammation could also derive from genome instability in the neuronal or glial populations of the brain. Recent literature has provided substantial evidence supporting the notion of DNA damage driven neuroinflammation. Two main pathways have so far been described; The DDR-driven activation of NF-κB [115–117], or the cytosolic nucleic acid-mediated antiviral like response [99,118–124]. In the first case, DDR triggers the formation of the ATM-NEMO complex, which translocates to the cytoplasm, releasing NF-κB from Ikβ (Fig. 2). Notably, Atm haploinsufficient $Ercc1^{-/\Delta}$ mice displayed decreased NF-κB activation and improved neurological phenotypes, emphasizing the connection between DDR and NF-κB-driven inflammation [125]. In the second case, cytoplasmic nucleic acids -including cytosolic chromatin fragments [119–121,124], R-loop-derived RNA-DNA hybrids [99,126], and ruptured micronuclei [122,123]- accumulate when cells are exposed to genotoxic stress [127–129]. These nucleic acids are recognized by nucleic acid sensors like Toll-like receptor 9 (TLR9), Absent In Melanoma 2 (AIM2), or Retinoic Acid Inducible Gene-1 (RIG1) and Cyclic GMP-AMP synthase (cGAS) (Fig. 2) [130]. Recent evidence links mitochondrial-dependent DNA activation of microglial TLR9, which mainly binds endosomal dsDNA [131] with dopamine neuron loss in a model of Parkinson's disease [132]. Inflammasomes, which assemble after dsDNA mediated activation of AIM2 [133] play a role in multiple sclerosis, although recent evidence suggest an inflammasome-independent role of AIM2 during the disease [134], whereas elevated levels of the RIG-1-like receptor family, which detects uncapped RNA or long, double-stranded RNA molecules [135] were detected in the cortex of AD patients [136].

The cGAS–STING signaling pathway has been identified as a pivotal mediator of inflammation linking genome instability with neuroinflammation. cGAS is a cytosolic DNA sensor that plays a crucial role in the innate immune system. Its primary function is to detect the presence of cytoplasmic DNA, which may arise from various sources such as viral infections, cellular damage, or aberrant cellular processes. When cGAS recognizes dsDNA in the cytoplasm, it catalyses the synthesis of a second messenger molecule called cyclic GMP-AMP (cGAMP). STING is located in the endoplasmic reticulum membrane, and its activation is triggered by the binding of cyclic dinucleotides, such as cGAMP. Activated STING recruits a protein kinase called TANK-binding kinase 1 (TBK1) to the endoplasmic reticulum membrane. TBK1 then phosphorylates a transcription factor called interferon regulatory factor 3 (IRF3) (Fig. 2). Phosphorylated IRF3 translocates to the nucleus of the cell to induce the transcription of genes encoding type I interferons and other pro-inflammatory cytokines. [137,138]. In turn, the transcribed interferons and cytokines are then synthesized and released from the cell, serving as signaling molecules that alert neighboring cells and coordinate the immune response. The expression levels of the cGAS-STING pathway are limited in neuronal populations [139]. Despite that, neurons bearing DSBs were shown, using single-nucleus and transcriptomic techniques, to activate NF-κB-mediated antiviral immune pathways, subsequently activating microglial cells (Fig. 2) [140]. Additionally, it has been pointed out that cytosolic mitochondrial DNA fragments in neurons can elicit an inflammatory response through activation of the cGAS-STING in ALS [141]. On the other hand, microglia has a potent cGAS-STING protein machinery for cytosolic nucleic acid sensing and although post-mitotic and long-lived neurons are more susceptible to DNA lesions, the brain's immune cells can also amass DNA damage, jeopardizing neuronal homeostasis. Specifically, the prolonged lifespan of microglia makes them prone to progressively accumulating oxidative DNA lesions over the course of the lifespan [142,143]. Recent data highlight the critical role of the microglial cGAS-STING pathway in driving neuroinflammation. Specifically, the activation of STING in microglia due to mitochondrial disturbances has been linked to neurodegeneration and cognitive decline. [144]. Previous reports have also demonstrated that insufficient DNA repair in $Atm^{-/-}$ microglia results in the active export of AT-rich repetitive elements in the cytoplasm, activating the cGAS-STING pathway and inducing a type-1 interferon response [145,146].

Accumulation of DNA damage will ultimately lead to altered cellular homeostasis triggering cell death or cell-cycle arrest and senescence [147–150]. Although senescence is difficult to conceive in post-mitotic

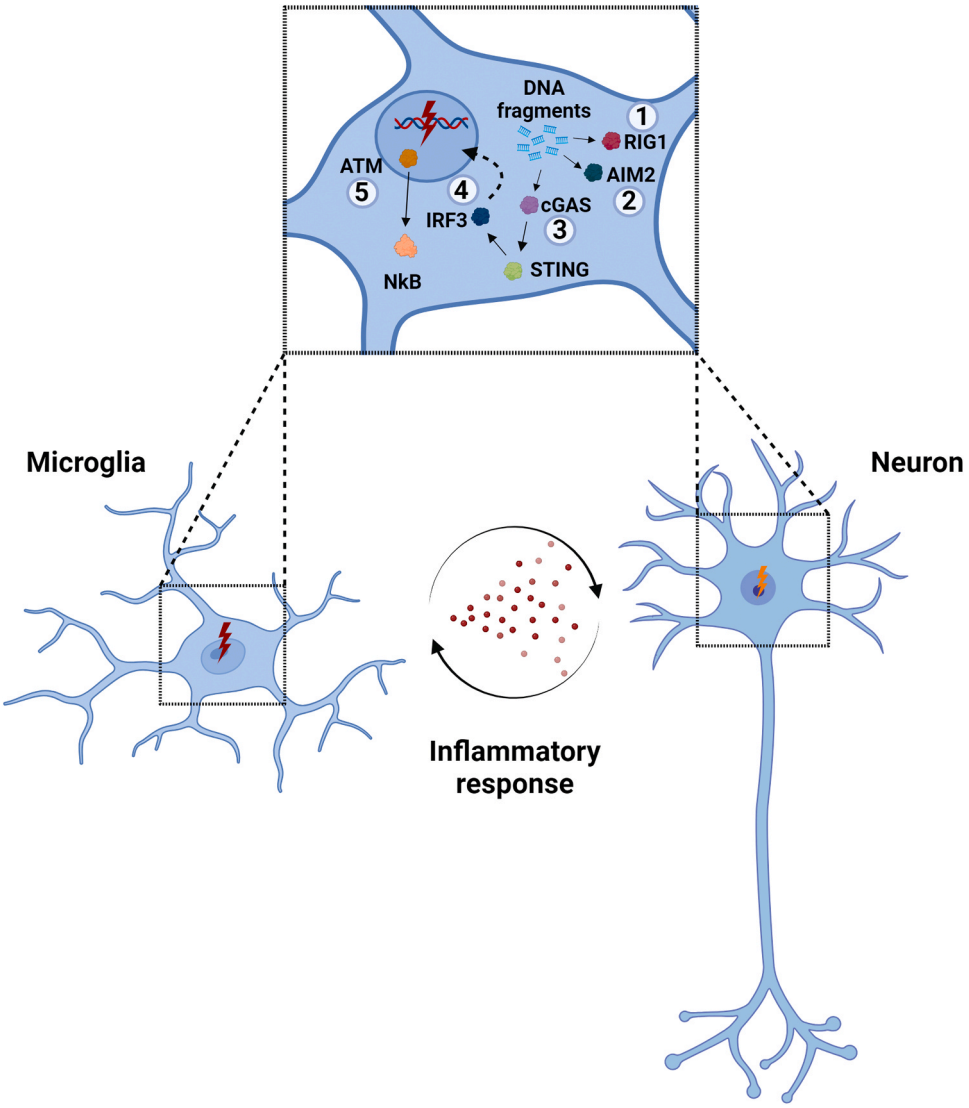

Fig. 2. DNA-damage mediated neuroinflammation. Neuroinflammation can be triggered by DNA damage either in microglia or in neurons. DNA damage can lead to the release of chromatin fragments into the cytoplasm. These cytosolic fragments are recognized by RIG1 (1) and AIM2 (2) triggering the proteolytic activation of IL-1β and IL-18. cGAS also binds to cytosolic fragments (3) and activates STING, inducing the nuclear translocation of IRF3 (4). Additionally, NF-kB can be directly activated by the DNA damage sensor ATM (5). Figure was created with Biorender.com.

cells as neurons [151], yet a plethora of studies support the presence of senescent neurons, as well as astrocytes in brains of aged humans and mice [152–155] and of patients with NDDs [156–161]. On the other hand proliferation of microglia cells in neurological disorders [162] has been linked with acquired senescent phenotypes [163]. In all cases, the presence of senescent populations in brain is linked with secretion of proinflammatory cytokines (SASP) that also contribute to the inflammation phenotype [164]. Consistently, the elimination of $p16^{Ink4a}$-expressing microglia from aged mice has been shown to ameliorate the neuroinflammatory phenotype [155]. Interestingly recent data have linked the cytosolic sensors cGAS-STING with the induction of the senescence related secretory phenotype [129,144].

DNA damage-driven inflammation in microglial cells, whether through cytoplasmic nucleic acid sensing and DDR-mediated activation of NF-κB or through acquired senescent phenotypes, plays a critical role in the initiation and progression of neurodegeneration. Understanding the mechanisms that govern the interaction between inflamed microglia and various neuronal populations is essential for gaining insights into the molecular pathways underlying neurodegeneration.

5. Conclusions and future perspectives

The intricate relationship between DNA damage and neurodegenerative diseases underscores the pivotal role of genomic instability in the pathogenesis of these debilitating conditions. DNA damage, whether in the form of DSBs or oxidative lesions, can act as a trigger for neuroinflammation and the premature onset of senescent-like phenotypes in neurons. This cascade of events, observed in both AD and the aging central nervous system, emphasizes the broader implications of compromised genome integrity in the context of neuronal health. It remains to be seen whether targeting key players in the DDR, such as p21 and ATM or exploiting strategies to boost DNA repair [165] holds promise in mitigating the impact of genomic instability on neuronal function. Additionally, the identification of microglia as central contributors to neuroinflammation opens avenues for promising interventions. The recent advancements in single-nucleus RNA sequencing and insights into the cGAS-STING pathway further provide potential targets for therapeutic intervention in the context of DNA damage-mediated neuropathology. Ultimately, the evolving landscape of therapeutic strategies provides hope for a future where the impact of

DNA damage on neuronal health can be alleviated, offering improved outcomes and quality of life for those facing these challenging conditions.

CRediT authorship contribution statement

George A. Garinis: Writing – review & editing, Conceptualization. **Ioanna Stavgiannoudaki:** Writing – original draft. **Evi Goulielmaki:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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