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Review

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The DNA damage response - from cell biology to human disease

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Abstract

Maintenance of DNA integrity is crucial for faithful transmission of the genetic code from generation to generation. Our genetic code is constantly under attack from both endogenous and exogenous sources of DNA damage. To ensure genome stability, cells have developed elegant DNA damage repair mechanisms. Defects in DNA damage repair have been linked to several human diseases including promoting oncogenesis, heritable neurodegenerative and neuromuscular diseases caused by unstable DNA repeats, neuropathies and myopathies caused by mutations and rearrangements in mitochondrial DNA, neuropsychiatric disorders, and heritable premature aging syndromes. This review will discuss our current understanding of how these underlying errors in DNA repair contribute to the clinical outcomes of patients who present with these diseases.

Keywords: DNA damage response, DNA damage repair, mutagenesis, cancer, neurodegeneration, neuropsychiatric disorders, premature aging, clinical outcomes

INTRODUCTION

Cells in our body are exposed daily to endogenous and exogenous sources that damage their DNA, which, if left unrepaired, can lead to genome instability as these errors are perpetuated over subsequent cellular divisions[1]. It has been estimated that approximately 10^5 DNA lesions are generated spontaneously each day

in the mammalian genome[2]. Endogenous sources of DNA lesions include the production of reactive oxygen and nitrogen species through oxidative respiration, byproducts of lipid peroxidation, endogenous alkylating agents, estrogen and cholesterol metabolites, reactive carbonyl species, as well as spontaneous disintegration and hydrolysis of DNA under physiologic conditions leaving non-coding apurinic/apyrimidinic abasic sites[3,4]. Exogenous sources include ultraviolet (UV) light from the sun, ionizing radiation (IR), genotoxic chemicals, and carcinogens that are inhaled or ingested[5]. It has been postulated that one day of sun exposure can cause up to 10^5 UV-induced DNA lesions in each exposed keratinocyte, with the release of oxidative damage locally that can induce inflammation[2].

Unrepaired DNA damage can induce cancer-causing mutations, cell death or senescence, and aging. The type of damage leads to distinct phenotypes and the activation of specific repair pathways. DNA lesions can cause roadblocks for the transcription and replication machinery, errors in gene transcription, changes in the epigenetic landscape, and dysregulation of the cell cycle. Damage caused by double-strand breaks (DSBs) is considered one of the major causes of genomic instability if left unrepaired, as they can lead to recombinatorial replication events that form cancer-prone chromosomal translocations and other chromosomal aberrations including aneuploidy and loss of heterozygosity[5]. Cells have developed sophisticated mechanisms to identify and repair damaged DNA in order to maintain genome stability. These involve multiple signaling pathways focused on the type of DNA lesion [i.e., DSB, single-strand break (SSB), inter-strand crosslink (ICL)], phosphorylation of damage sensing proteins and signaling kinases, recruitment of repair proteins to sites of damage, triggering cell cycle checkpoints and downstream effectors that allow for lesional repair, or activation of apoptotic or senescence pathways to ensure faithful transmission of genetic information to their progeny[6]. Loss of function of these repair pathways leads to characteristic human disease phenotypes, underlying the importance of DNA damage repair in the maintenance of human health and homeostasis.

DNA DAMAGE RESPONSE (DDR) AND REPAIR PATHWAYS

Mammalian cells have developed an evolutionarily conserved and sophisticated DNA damage response (DDR) to identify and repair damaged DNA in order to protect their genetic code for faithful replication and transmission of genetic information to future progeny[6,7]. This DDR repair pathway consists of families of proteins that serve as *sensors* of damage, *mediators* of the response, further recruitment of *transducers* that enable downstream signaling of *effectors*, which activate cell cycle checkpoints to allow for repair, or trigger apoptosis or senescence, to prevent transmission of erroneous genetic information to daughter cells. Many of these proteins have been implicated in human disease. As an in-depth discussion of the DDR is beyond the scope of this article, a concise review of the different repair pathways will be provided below as a primer to the readers. This will follow with comprehensive sections on the etiopathogenesis of human diseases associated with errors in DNA damage repair (summarized in Table 1).

Double-strand break (DSB) repair

DSBs are formed following exposure to IR, X-rays, chemotherapies, and free radicals[8]. The presence of DSBs is considered to pose the greatest threat to genome stability in mammalian cells[9]. Repair of DSBs occurs via two pathways: the efficient, but error-prone, non-homologous end-joining (NHEJ) pathway; or the less efficient, but less error-prone, homologous recombination (HR) pathway[10,11]. NHEJ functions during the G_1 phase of the cell cycle and repairs breaks by the simple joining of free ends, which increases the risk of mutagenesis. Activation of NHEJ requires the recruitment of the phosphoinositol-kinase-kinase-kinase (PI3K) ataxia telangiectasia mutated (ATM) to sites of DSBs, leading to phosphorylation of the histone variant H2A.X (γH2AX) next to the break sites, which can be propagated over kilobase distances, forming γH2AX DNA damage foci[12]. These foci serve as beacons to recruit downstream repair and effector

Table 1. Human diseases associated with deficient mechanisms of DNA damage repair. List of syndromes caused by mutations in genes involved in DNA damage repair categorized by syndrome, DDR pathways affected, associated mutations in DDR genes, and presenting symptoms.

Disease	Affected DDR Mechanism	Affected Gene(s)	Disease Prevalence	Phenotype
(1) Cancer syndromes				
Ataxia-Telangiectasia[43,152]	DSB repair	*ATM*	1 in 40,000-100,000 live births	Lymphomas, leukemias, breast cancer
Ataxia Telangiectasia-Like Disorder[153]	DSB repair	*MRE11*	Rare	Leukemias
Bloom Syndrome[96,97,154]	HR repair	*BLM*	Overall prevalence is unknown; estimated 1 per 48,000 births in the Ashkenazi Jewish population	Carcinomas, leukemias, lymphomas
Fanconi Anemia[30,32,155]	ICL repair, HR	*FANCA-C, FANCD1, D2, FANCE-G, FANCI, J, L-N*	1 in 136,000 newborns, varies from 1 in 100,000 to 250,000 births	Leukemia, myelodysplasia, squamous cell carcinoma
Hereditary Breast and Ovarian Cancer Syndrome[156,157]	HR repair	*BRCA1, BRCA2*	Estimated 1 in 333 to 500 individuals have a BRCA1/2 mutation	Breast and ovarian cancers
Hereditary Nonpolyposis Colorectal Cancer[158-160]	MMR	*MSH2, MSH6, MLH1, PMS2*	2%-5% of the Caucasian population	Colorectal cancer, carcinomas
Li-Fraumeni Syndrome[161,162]	DSB repair	*TP53*	Not well established, one group reported prevalence at 1:3,555 to 1:5,5476	Gliomas and breast cancers, sarcoma
MYH-Associated Polyposis[163-165]	BER, oxidative damage repair	*MYH*	Responsible for 7% of attenuated adenomatous polyposis and 6.6% of classic polyposis cases	Colorectal cancer
Nijmegen Breakage Syndrome[117,166,167]	DSB repair	*NBS1*	1 in 100,000 newborns worldwide	Lymphomas
Rothmund-Thomson Syndrome[101]	BER, HR?	*RECQL4*	Prevalence is unknown; about 300 cases have been reported in the literature	Osteosarcoma
Werner Syndrome[99,168,169]	BER, HR, telomere maintenance	*WRN*	1 in 200,000 in the US, estimated 1 in 30,000 people in Japan and Sardinia	Various cancers (thyroid, melanoma, soft tissue sarcoma, osteosarcoma)
Xeroderma Pigmentosum[2,170,171]	TC-NER	*XPA-G, POLH*	1 in 1,000,000 in US and Europe, about 1 in 22,000 in Japan	UV-induced skin cancers
(2) Neurologic syndromes				
Aicardi Goutieres Syndrome[172,173]	Damage signaling	*RNASEH2, TREX1*	1 to 5 per 10,000 live births	Cerebral atrophy, intracranial calcifications, microcephaly, neurodegeneration
Ataxia Telangiectasia[43,152]	DSB repair	*ATM*	1 in 40,000-100,000 live births	Cerebellar ataxia, neurodegeneration, oculomotor apraxia
Ataxia Telangiectasia-Like Disorder[153]	DSB repair	*MRE11*	Rare	Cerebellar ataxia, neurodegeneration, oculomotor apraxia
Ataxia with Oculomotor Apraxia Type 1[64,77]	SSB repair	*APTX*	A rare disease, most frequent in Portugal and Japan	Cerebellar ataxia, neurodegeneration, oculomotor apraxia
Ataxia with Oculomotor Apraxia Type 2[174,175]	SSB repair, R-loop resolution	*SETX*	Estimated 1 in 900,000 individuals worldwide	Cerebellar ataxia, neurodegeneration, oculomotor apraxia
Cerebro-Ocular Facio-Skeletal syndrome[176,177]	TC-NER	*CSB, XPD, XPG, ERCC1*	Rare - fewer than 20 cases confirmed	Brain calcification, hypomyelination, microcephaly, neurodegeneration
Cockayne Syndrome[87,178]	TC-NER	*CSA, CSB, XPB, XPD, XPG*	Less than 1 case per 250,000 live births in the US	Microcephaly, demyelination, neurodegeneration
Dyskeratosis Congenita[179]	Telomere maintenance	*DKC1, TERC*	Prevalence is unknown; more than 400 families were reported in the world	Microcephaly, cognitive impairment, developmental delay
Microcephaly, Intractable	NHEJ, SSB repair	*PNKP*	Rare, prevalence unknown	Microcephaly, seizures, growth

Seizures, and Developmental Delay Syndrome [180-182]				defects
Seckel Syndrome[139,183]	DSB repair, replication fork repair	*ATR, PCTN, SCKL2, SCKL3*	Less than 1 in 1,000,000	Microcephaly, cognitive impairment, developmental delay
Spinocerebellar Ataxia with Axonal Neuropathy[75]	SSB repair	*TDP1*	Rare	Cerebellar ataxia, neurodegeneration
(3) Aging syndromes				
Ataxia-Telangiectasia[43,152]	DSB repair	*ATM*	1 in 40,000-100,000 live births	Premature bone marrow exhaustion, early-onset diabetes, neurodegeneration
Alpers-Huttenlocher Syndrome[184]	Mitochondrial DNA replication and repair	*POLG1*	1 in 100,000 individuals	Neurodegeneration, liver failure
Bloom Syndrome[96,97,154]	HR repair	*BLM*	Overall prevalence is unknown; estimated 1 per 48,000 births in the Ashkenazi Jewish population	Early-onset diabetes, pulmonary disease, increased cancer risk
Cockayne Syndrome[86,87,178]	TC-NER	*CSA, CSB, XPB, XPD, XPG*	Less than 1 case per 250,000 live	Cataracts, muscle atrophy, neurodegeneration
Fanconi Anemia[30,32,155]	ICL repair	*FANCA-W*	1 in 136,000 newborns, varies from 1 in 100,000 to 250,000 births	Premature bone marrow exhaustion, increased cancer risk
Hutchinson-Guilford Progeria Syndrome[185,186]	DDR, DSB repair, chromatin organization	*LMNA*	Approximately 1 in 20,000,000	Alopecia, atherosclerosis
Werner Syndrome[99,168,169]	BER, HR, telomere maintenance	*WRN*	1 in 200,000 in the US, estimated 1 in 30,000 people in Japan and Sardinia	Growth retardation, short stature, premature graying of hair, alopecia, arteriosclerosis, atrophic skin, bilateral cataracts, type II diabetes
(4) Immunodeficiencies				
Hyper-IgM Syndrome[112]	CSR	*AID, UNG*	Fewer than 1 in 1,000,000	Increased IgM levels, lymphoid hyperplasia
Immunodeficiency with Microcephaly[1,187]	NHEJ	*XLF*	Less than 1 in 1,000,000 worldwide	Hypogammaglobulemia, lymphopenia, microcephaly
Ligase IV Syndrome[82,188]	NHEJ	*LIG4*	Prevalence is unknown; globally only 28 cases are described	Hypogammaglobulemia, lymphopenia[188]
Radiosensitive Severe Combined Immunodeficiency[187]	NHEJ	*ARTEMIS*	Rare	Agammaglobulinemia, lymphopenia
Schimke Immuno-Osseous Dysplasia [189]	Replication fork repair	*SMARCAL1*	1 in 1,000,000 to 3,000,000 people in North America	T cell deficiency
Severe Combined Immunodeficiency Syndrome[154,187]	NHEJ	*Rag1, Rag2*	1 in 100,000 in US	Agammaglobulinemia, lymphopenia

DDR: DNA damage response; DSB: double-strand break; HR: homologous recombination; ICL: Interstrand crosslink; MMR: mismatch repair; BER: base excision repair; TC-NER: Transcription-coupled nucleotide excision repair; SSB: single-strand break; NHEJ: non-homologous end-joining; CSR: class-switch recombination.

proteins to sites of damage, leading to activation of the G_1 cell cycle checkpoint kinase Chk1 and cell cycle arrest in a p53-dependent manner[13]. HR requires a template sister chromatid for accurate alignment and annealing of DSBs and thus occurs during the G_2 and S phases of the cell cycle. Phosphorylation of H2A.X during HR requires the PI3K ataxia telangiectasia related (ATR) and subsequent recruitment of key proteins such as BRCA1 and BRCA2 to the replication fork for DNA template repair. Mutations in *BRCA1/2* (breast cancer gene 1/2) have been linked to familial breast cancer syndromes[14,15].

Nucleotide excision repair

Nucleotide excision repair (NER) is the most versatile repair pathway with the ability to repair damaged SSBs and other lesions caused by UV, chemical-induced DNA adducts, crosslinks, and oxidized bases[16].

Two NER pathways have been identified in eukaryotes in response to distinct types of DNA lesions: the general genome NER (GG-NER) pathway responds to genome-wide DNA damage and requires the xeroderma pigmentosum (XP) complementation group C/Human Homolog of Rad23 B (XPC/HHR23B) complex[17]; and transcription-coupled NER (TC-NER), which exclusively repairs lesions identified on single-stranded DNA templates during transcription and requires recruitment of Cockayne Syndrome (CS) A and B (CSA and CSB) proteins to stalled RNA polymerase II at lesion sites[18-20]. Mutations in *XPC* have been associated with photosensitivity and predisposition to cancers in patients with XP[21], while patients harboring mutations in *CSA* and *CSB* present with developmental growth delays and deformities, thought to be due to dysregulated transcription[22].

Base excision repair

Base excision repair (BER) responds to damage caused by byproducts of cellular metabolism including the formation of reactive oxygen species (ROS), methylation, deamination, and hydroxylation[23]. This pathway recognizes and repairs abasic sites, SSBs, and damaged nucleotide bases[24]. There have been no known human disorders associated with BER deficiency to date, suggesting that there are likely redundancies in the BER pathway that allow for safeguards against genome instability. However, loss of function of core BER pathway proteins in mice is embryonic lethal, highlighting the importance of this pathway[5]. Certain polymorphisms in the BER pathway scaffold protein XRCC1 may appear to be associated with lung and other cancers, pointing to the possible involvement of this pathway in regulating oncogenesis[25].

Mismatch repair

Errors in base-pairing or small in-frame deletions (indels) made by DNA polymerase are identified and corrected by the mismatch repair (MMR) system to ensure faithful replication of the genetic code[26]. Mismatches or indels are repaired by a heterodimeric complex requiring the proliferating cell nuclear antigen ring protein[27], which serves as a sliding clamp along a coding strand template of the DNA replication fork to recruit the MMR assembly composed of MSH2, MSH3 and/or MSH6 (MutS Homolog 2/3/6), MLH1 (MutL Homolog 1), EXO1 (Exonuclease 1), and DNA polymerases[28]. Defects in MMR lead to microsatellite instability, as seen in hereditary nonpolyposis colorectal cancer (HNPCC) and other sporadic cancers[29].

Interstrand crosslink repair

The formation of interstrand crosslinks (ICLs) between two strands of DNA causes roadblocks for both the transcription and replication machinery leading to transcriptional and/or replication stress. Due to the complex structure of ICLs, several steps and a multitude of enzymes and protein complexes are required to remove these lesions from damaged DNA and enable repair. Core to this repair machinery is the members of the Fanconi anemia (FA) pathway, 13 of which are mutated in FA syndrome[30,31]. Central to the recognition and repair of ICLs is the ID (FANCI-FANCD2) complex, which accumulates at sites of ICLs and recruits FA enzymes including the FAN1 endo- and exo-nuclease, translesional synthesis polymerases REV1 and Polζ, and FA proteins BRCA2/FANCD1, PALB2/FANCN, and BACH1/FANCJ in an ATR-dependent manner to facilitate HR repair of excised ends[10]. FA patients with mutations in FA proteins present with increased cancer risks and premature bone marrow failure[32].

THE ROLE OF PHYSIOLOGICAL DNA DAMAGE IN BIOLOGICAL PROCESSES

V(D)J recombination, class-switch recombination, and somatic hyper-mutation

Certain biological processes depend on programmed DNA damage. Immature T lymphocytes rely on DSB formation at exons encoding the variable regions used for antigen recognition and binding on T cell receptors (TCR) during V(D)J recombination. Recognition of cleavage sequences flanking these V, D, and J exons by the RAG1-RAG2 complex leads to the formation of blunt-ended DSBs, which are recombined and

repaired using NHEJ[33,34]. These recombination events increase the T cell repertoire and TCR diversity, ensuring healthy and active immune surveillance. Subsequently, defects in NHEJ cause severe combined immunodeficiency syndrome (SCID)[35]. Immature B cells have a rearranged immunoglobulin (Ig) heavy-chain variable domain that is initially fused to an Igμ constant region. During antigen-stimulated B-cell differentiation, class-switch recombination (CSR) juxtaposes a V region to any constant region to encode distinct antigenic memory on the resultant differentiated Ig. Antigenic stimulation of B cells also activates somatic hypermutation to increase mutation rates in the heavy- and light-chain variable regions to expand the repertoire of variable segments to allow for the selection of B cells that express Ig molecules with high antigen specificity. CSR and somatic hypermutation require activation-induced deaminase, which targets the variable-region exons and IgH switch regions, causing deamination of cytosine residues to uracil and the formation of U:G mismatches, triggering repair through the MMR or BER pathways to form SSBs. It is thought that SSBs formed during CSR are converted to DSBs and repaired using NHEJ to ligate the variable region to a constant region, while SSBs formed during somatic hyper-mutation are repaired in an error-prone manner to yield mutations within the variable regions[34].

Meiotic recombination

The exchange of genetic information during meiosis is crucial to allow for genetic diversity and gamete formation. Chromosomal alignment and exchange of genetic information between homologous chromosomes during phase I of meiosis requires the formation of DSBs generated by Spo11[36]. The Mre11-Rad50-Nbs1 (MRN) complex is recruited to sites of damage and resects the DSBs to form ssDNA, which can be repaired by HR using the homologous chromosome and requires the meiosis-specific RAD51-like protein DMC1[37]. Spo11 or Dmc1 knockout mice are viable but infertile[38].

Telomere maintenance

The ends of mammalian chromosomes are organized into telomeres - stretches of short tandem DNA repeats terminating in a 3' ssDNA overhang that is sequestered in a Shelterin complex which prevents access by the NHEJ or HR machinery[39-41]. However, during the G_2 phase of the cell cycle, exposed telomeres can be recognized by the MRN complex and ATM to possibly encourage a localized DDR for telomere end-processing and shelterin complex formation[42]. Along these lines, loss of function of several proteins involved in the DDR causes telomere shortening and dysfunction that can trigger chromosomal fusions and chromosomal instability[41,43].

Human cells normally do not express enough telomerase to withstand naturally occurring telomere shortening due to the inability of the DNA replication machinery to fully replicate the ends of chromosomes, leading to open terminal ends of chromosomes that are perceived to be DSBs and are subjected to repeated cycles of breakage and repair[44]. These cycles can lead to apoptosis or senescence, and are also believed to contribute to the aging process and other age-related pathological processes such as atherosclerosis and arthritis[45].

HUMAN DISEASES CAUSED BY ERRORS IN DNA DAMAGE REPAIR

Cancer syndromes

Cancer is considered to be a disease of genome instability and mutation caused by errors in DNA damage repair[5,46,47]. Cytogenetics analysis of cancer cells often reveals chromosomal instability, copy number alterations, and expansions or contractions of repetitive microsatellite sequences[46]. Evidence that errors in DNA damage maintenance are linked to cancer development lies in the fact that mutations in several DDR genes are linked to several cancer syndromes [Table 1].

Point mutations in the HR pathway genes *BRCA1* and *BRCA2* predispose women to hereditary breast and ovarian cancer (HBOC) syndrome[14,48]. HBOC accounts for up to 10% of breast cancer cases - individuals that are heterozygous carriers of *BRCA1/2* mutations have a 40-80% lifetime risk of developing breast cancer[49] while male patients who harbor *BRCA1/2* mutations have an increased risk of developing breast, pancreas, and prostate cancers[50-52]. Familial mutations in HR pathway genes *BACH1, PALB2*, and *RAD51C* have also been identified in 3% of familial breast cancer patients and confer a 2-fold increased risk of developing breast cancer[53], while mutations in key genes involved in DSB repair including *CHK2*, *ATM*, *NBS1*, and *RAD50* have been shown to also confer a 2-fold increased risk of breast cancer[54].

Heterozygous mutations in MMR pathway genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* have been linked to HNPCC, or Lynch Syndrome[55]. Patients present primarily with colorectal cancer but also have an increased predisposition to developing endometrial, ovarian, gastric, and renal carcinomas.

FA is a genetic syndrome characterized by mutations in 13 FA genes (*FANCA* to *FANCV*) involved in the ICL repair pathway. Monoallelic inactivation of *FANCD1*(also known as *BRCA2*) leads to adult HBOC cancer predisposition syndrome with an increased lifetime risk of breast cancer by 50% and a 15% increased lifetime risk of ovarian cancer (reviewed in Nalepa & Clapp)[56]. A review of The Cancer Genome Atlas has identified acquired mutations, epigenetic silencing, and copy number variations in *FA* genes have been identified in patients with a variety of malignancies[57].

Environmental sources of DNA damage and tumorigenesis

Benzo(α)pyrene in cigarette smoke has been shown to react with the 2-amino position of guanine residues, forming a guanine adduct, which after one cycle of DNA replication, leads to the incorporation of an adenine base instead of cytosine and subsequent guanine to threonine tranversion[58]. This transversion causes a mutational profile in the tumor suppressor gene *TP53*, which strongly correlates with lung cancer in smokers *vs.* non-smokers[59]. Environmental sources of IR or X-rays produced by cosmic radiation, soil, rocks, radioactive materials, and medical devices can lead to direct DNA damage or indirect DNA damage by radiolysis of water molecules to form reactive hydroxyl radicals[8]. IR can lead to base damage, DSBs, and SSBs, all of which require prompt repair via the BER and HR pathways[60]. Repair of UV sunlight-induced DNA crosslinks requires the XP family member of proteins involved in the BER pathway[61]. Hereditary mutations in these genes lead to the familial syndrome with their namesake XP, in which patients present with premature skin photoaging and an increased incidence of skin cancer[62]. Lifetime ingestion of carcinogens including polycyclic aromatic hydrocarbons, nitrosamines in cured foods, aldehydes in alcohol, and arsenic in contaminated drinking water, has been implicated in the development of colorectal cancers[63].

Neurological diseases

Until recently, it has been thought that post-mitotic neurons rely solely on error-prone NHEJ for DNA repair, but recent reports now suggest that neurons are able to use a transcription-triggered, replication-independent recombination repair pathway that requires the HR repair protein RAD52 for the repair of DSBs[64,65]. As neurons are obligative aerobes, they rely heavily on oxidative phosphorylation via mitochondrial respiration, which leads to the production of ROS that can cause DNA damage[43]. Defects in DDR repair in neurons lead to neurodegenerative syndromes that primarily affect the oxygen-dependent cells of the cerebellum[66]. Patients present with ataxia (loss of motor coordination), oculomotor apraxia (disco-ordinated eye movements), and dysarthria (speech deficits). Perhaps the most extensively studied central nervous system disease caused by a DDR defect is Ataxia-Telangiectasia (A-T), caused by mutations in ATM[67]. A-T patients have progressive loss of Purkinje and granule cells in their cerebellum, leading to rapid loss of motor coordination with early onset in their childhood years[67]. Similarly, patients with A-T-

like Syndrome (A-TLD) have mutations in *MRE11*, a member of the MRN complex which senses the presence of DSBs and recruits ATM to amplify the DDR, and present with motor deficits similar to patients with A-T, albeit with a delayed onset and slower progression[10].

Patients with DDR syndromes often present with an abnormally small head circumference (microcephaly), thought to be due to defective proliferation of neuroprogenitor cells during fetal development[68]. A hypomorphic mutation in the *ATR* gene is found in patients with Seckel Syndrome (SS) - these patients present with a constellation of findings including dwarfism and a "bird-like" facies. Loss of function of *ATR* in cells leads to a decreased ability to repair replication stress-induced DNA damage through HR[68]. Patients with defects in HR, such as Bloom Syndrome (BS) patients (who have mutations in the RECQ helicase BLM), FA patients, and patients with XFE Progeroid Syndrome (who have XPF mutations), also present with microcephaly[68]. Other microcephalic syndromes that are associated with defects in the ATR DDR pathway include Miller-Dieker Lissencephaly and Williams-Beuren Syndrome[69]. Patients with Nijmegen Breakage Syndrome (NBS) and Nijmegen Breakage Syndrome-Like Disorder (NBSLD) have hypomorphic mutations in *NBS1* and *RAD50*, respectively, members of the aforementioned MRN complex that are involved in DSB repair[70,71]. Interestingly, NBS and NBSLD patients do not present with the same findings as patients with A-T despite having mutations in genes that are involved in the ATM DDR pathway; however, NBS mutant neurons exhibit ATM-dependent apoptosis, suggesting that a robust ATM response may decrease the severity of neurodegeneration and microcephaly in these patients[72]. Finally, pregnant survivors of the Hiroshima and Nagasaki atomic bombs were found to deliver fetuses with microcephaly and smaller brain volume, emphasizing the deleterious effects of in utero exposure to large doses of IR[73].

The necessity of non-dividing, post-mitotic neurons to rely on SSB repair (SSBR) machinery has led to the identification of several neurological disorders associated with mutations in members of the SSBR pathway[74]. A histidine to arginine mutation at residue 493 (H493R) in tyrosyl-DNA phosphodiesterase, the enzyme that hydrolyzes the tyrosyl-3' phosphate linkage in order to resolve stalled topoisomerase 1-DNA complexes during SSBR, was identified in patients with hereditary Spinocerebellar Ataxia Axonal Neuropathy type 1 (SCAN1)[75]. SCAN1 patients present with progressive childhood-onset of cerebellar ataxia followed by areflexia and peripheral neuropathy[76]. Similarly, germline mutations in the SSBR pathway protein APTX have been linked to individuals with Ataxia Ocular Motor Apraxia type 1 (AOA1), a progressive neurological disorder that resembles other types of cerebellar ataxia including A-T[77,78]. APTX nuclease cleaves AMP from the 5'-terminal of ssDNA breaks, thus allowing for ligation of the 5'-phosphate terminus[79]. Mutant APTX in terminally differentiated cells such as neurons may lead to the accumulation of ssDNA breaks, creating transcriptional blocks and increased transcriptional stress, triggering apoptosis. Indeed, fibroblasts from AOA1 patients are more sensitive to oxidative DNA damage and there is more oxidative DNA damage in the cerebellum of AOA1 patients[80]. Finally, biallelic mutations in exon 12 of the SSBR scaffold protein XRCC1 (K431N) lead to axonal neuropathy and cerebellar ataxia in patients with AOA type 5[81]. Taken together, these findings support the role of dysfunctional DDR in the etiopathogenesis of neurologic diseases. A summary of these neurological diseases is provided in Table 1.

Patients with missense mutations in DNA ligase IV (LIG IV) can present with microcephaly, growth retardation, pancytopenia, a predisposition to lymphomas, combined immunodeficiency, and hypersensitivity to chemotherapies[82]. This is similar to patients with mutations in XLF, who present with milder symptoms of radiosensitivity, pancytopenia, and impaired survival[83]. Loss of function of XRCC4 has been reported in a patient with microcephaly and cerebellar ataxia with an intact immune system,

suggesting that this protein is not essential for V(D)J recombination[84].

Aging

Aging is a complex process thought to consist of a gradual decline in mitochondrial function, metabolic dysregulation, the loss of stem cell function, and the accumulation of damaged macromolecules within cells[85]. Evidence that the accumulation of DNA damage can lead to premature aging lies in several premature aging syndromes that are linked to defects in DDR pathways, including: progeroid syndromes like Cockayne Syndrome (CS), Trichothiodystrophy (TTD), Cerebro-Oculo-Facio-Skeletal Syndrome (COFS), Dyskeratosis Congenital (DKC); Hutchinson-Gilford Progeroid Syndrome (HGPS); Werner Syndrome (WS); Xeroderma Pigmentosum (XP); and Rothmund-Thomson Syndrome (RTS) [Table 1][1].

CS patients have mutations in *CSA* (also known as *ERCC8*) or *CSB* (also known as *ERCC6*) and present with early developmental growth retardation, progressive vision loss, sensorineural deafness, early-onset neurodegeneration, and an average life span of 12 years of age[22]. Approximately 70% of CS patients have a mutation in *CSA* and the remaining 30% have a mutation in *CSB*[86,87]. There are approximately 78 known *CSB* mutations and 30 *CSA* mutations, with patients harboring *CSA* mutations presenting with a more moderate form of CS[87]. Interestingly, despite defects in TC-NER being linked to mutations in *CS* genes, patients with CS do not present with UV hypersensitivity, nor have there been any reported cases of cancer in patients with CS, suggesting that repair defects in DNA damage alone are not sufficient to cause cancer but can promote premature aging[1]. This is in contradistinction to XP patients who also harbor defects in TC-NER due to mutations in XP genes, present with increased incidences of skin cancer, and can present with early-onset CS, combined XP/CS, and segmental progeria with features of dwarfism, cachexia, and microcephaly[88].

TTD patients have point mutations in the DNA helicases XPB and XPD, components of the repair and transcription factor IIH (TFIIH), causing them to suffer from progeria with CS features in addition to brittle hair, nails, and ichthyotic skin[88,89]. Mutant NER transgenic mice display signs of progeria, including accelerated aging, bony deformity, neurodegeneration, hearing loss, growth retardation, infertility, cachexia, stem cell depletion, and frailty, further emphasizing the role that NER plays in the aging process[90-92].

Defective GG-NER in XP patients caused by mutations in the NER repair enzymes XPA through to XPG leads to increased DNA damage across the entire genome[93]. Consequently, XP patients with GG-NER suffer from UV-induced skin hyperpigmentation with a 2000x increased risk of skin cancer as well as the development of tumors elsewhere in the body[93]. XP patients who also have defects in TC-NER present with rapid neurodegeneration[2,94].

Patients with mutations in the RECQ family of DNA helicases BLM, RECQL4, and WRN present with progeroid syndromes[95]. The BLM helicase suppresses recombination and maintains genome stability[96,97], RECQL4 participates in DNA replication and repair[98], and the WRN helicase manages replication stress and telomere stability[99]. Mutations in *BLM* cause BS, in which patients present with a shortened lifespan and early presentation of age-related diseases, including diabetes, chronic obstructive pulmonary disease, and cancer[100]. *RECQL4* mutations lead to RTS, presenting with juvenile cataracts, epidermal atrophy, and increased cancer risk[101]. *WRN* mutations cause WS with premature onset of age-related diseases, growth retardation, and lipodystrophy[102].

Immunodeficiency

Healthy immune surveillance is required to defend the body from foreign pathogens and antigens. Then, lymphoid B and T cells must be able to generate a diverse repertoire of B and T cell receptors (BCR and TCR, respectively). This relies on V(D)J recombination and CSR. To perform V(D)J recombination, cells require the recombinases RAG1 and RAG2[103]. These programmed DSBs are repaired in G_0/G_1 by NHEJ, requiring the damage sensing PI3K DNA dependent protein kinase to phosphorylate the exonuclease Artemis to process the breaks[104]. Repair by NHEJ requires ATM, the MRN complex, 53BP1 and RNF168[105]. These DSB repair proteins share overlapping functions with the DNA repair protein XLF[105]. End ligation is performed by the DNA LIG IV/XRCC4-XLF complex[106]. B cells undergo CSR to generate multiple Ig subsets and require activation-induced cytidine deaminase (AID) to deaminate cytidine to uracil at the transcriptionally active switch region, which is then modified by UNG (uracil-DNA glycosylase) to allow for BER[107].

Mutations in RAG1 or RAG2 lead to defective V(D)J recombination in T and B cells, resulting in severe SCID[108,109]. RAG1/2 deficient SCID patients are not radiosensitive and do not present with developmental delay but require stem cell transplantation in order to reconstitute their immune systems. In contrast, patients with mutations in the gene *DCLRE1C* that encodes for Artemis present with radiosensitive SCID and are predisposed to lymphoma[110].

Somatic mutations in *AICDA* and *UNG* affect CSR, resulting in hyper IgM gammopathy[111-113]. AID and UNG patients have lymph node hyperplasia due to the presence of giant germinal centers. AID patients may present with signs and symptoms of autoimmunity, inflammation, diabetes, arthritis, hemolytic anemia, immune thrombocytopenia, and chronic uveitis[112]. Defects in the chromatin remodeling and DDR complex INO80 affect CSR with reports of patients presenting with normal IgM but decreased IgG and IgA levels[114]. Constitutional MMR deficiency syndrome (CMMRD) presents with a partial Ig-CSR defect in which patients can present with brain tumors, hematological malignancies, and other solid organ cancers[115]. Somatic hypermutations in the MMR pathway genes *PMS2, MSH6, MSH2, or MLH1* have been detected in CMMRD patients[115]. Mutations in RNF168, which is responsible for ubiquitylation of 53BP1 and downstream recruitment of BRCA1 to DSBs[105], lead to defective DSB repair and Radiosensitivity, Immunodeficiency, Dysmorphic features, and Learning difficulties (RIDDLE) Syndrome[116]. Patients with RIDDLE syndrome have decreased IgG and IgA with clinical features of A-T[116]. Finally, patients with mutations in *NBS1*, a member of the MRN DSB repair sensor complex, present with NBS characterized by microcephaly, growth retardation, cognitive delay, immunodeficiency with a decreased complement of T and B cells, and increased cancer risk[117]. In summary, this diverse group of immunodeficiencies linked to mutations in DDR genes hits home the importance of preprogrammed DNA damage and repair for immune system maintenance (further outlined in Table 1).

USING ANIMAL MODELS TO STUDY HUMAN DISEASES OF DNA DAMAGE

To study the phenotype of deficient DNA repair, mouse models have been used extensively to model the symptoms found in many human diseases of DNA damage repair[118]. These murine models serve as invaluable tools to study the phenotypic effects of defects in DNA damage repair pathways at the cellular and whole organism levels; however, many of these models do not completely recapitulate the complexity of signs and symptoms that are seen in humans, and therefore, one must be aware of these limitations when conducting studies using these animal models. Listed below are several known genetically-engineered mouse models of human diseases of DNA damage:

(1) A-T mice faithfully recapitulate tissue radiosensitivity and immunodeficiency seen in patients with A-T; however, earlier mouse models lacked the typical neurological symptoms and cerebellar dysfunction seen in humans. A-T mice faithfully recapitulate tissue radiosensitivity...cerebellar dysfunction seen in humans[119-124]. A more recent report using the insertion recent report using the insertion of null mutations in both the *ATM* and *APTX* genes in a mouse model of A-T, successfully generated mice that developed severe ataxic symptoms and atrophy of the cerebellar molecular layer[125].

(2) Mouse models of HR deficiency require mutations in both alleles of *Brca1* or *Brca2* in order for mice to develop breast tumors while heterozygous deletions of either *BRCA1* or *BRCA2* are sufficient to drive tumorigenesis in humans[126-129].

(3) Mouse models of MMR deficiency are also tumor prone; however, unlike the hereditary colon cancer syndrome in human patients (Lynch syndrome), mice with mutations in MMR genes such as *Mlh1*, *Msh6*, and *Msh2* form tumors in the lymphatic compartment and not in the gut[130,131].

(4) Early mouse models of BS demonstrated that homozygous mutation of the murine BS gene *Blm* caused developmental delay and embryonic lethality[132].

(5) Several mouse models have attempted to model the complexity of FA, caused by mutations in more than a dozen genes involved in DNA interstrand crosslink repair. However, knockout mice with single-gene knockouts such as $FancA^{-/-}$ mice do not spontaneously display congenital anomalies nor have hematological abnormalities seen in FA patients[133]; however, $FancA^{-/-}$ and $FancG^{-/-}$ mice develop microcephaly due to increased neuronal apoptosis and can be interpreted as accelerated aging of stem cells in FA. Similarly, $FancC^{-/-}$ mice do not develop skeletal abnormalities or hematological abnormalities, but they do have impaired fertility, similar to that seen in FA patients, as well as hypersensitivity to DNA crosslinking agents[134,135].

(6) Mouse models of the progeroid diseases, Hutchinson-Gilford Progeria (HGP) and WS, do not have a marked progeroid phenotype, unlike the premature aging seen in patients. This has been postulated because mice have longer telomere lengths and may lead to relative resistance to the accelerated aging seen in WS patients with mutations in the *WRN* gene that encodes the BLM-related helicase[136]. Interestingly, mouse models of HGP harboring mutations in *LmnA*, a gene related to nuclear lamina and not to DNA repair pathways, also do not show signs of early aging, but HGP cells accumulate high levels of DNA damage[137,138].

(7) Seckel Syndrome (SS), a rare genetic condition caused by mutations in several genes, including genes involved in the ATR DNA damage repair pathway, namely *ATR* and *ATRIP*, presents with intrauterine growth restriction, dwarfism, microcephaly, and intellectual disability[139]. The mouse model harboring hypomorphic mutations on ATR recapitulates faithfully many of the features of SS patients and mice accumulate high amounts of DNA damage and genome instability in utero, leading to accelerated aging at birth[140].

(8) Mouse models of XP, defective in NER genes (*XPA*, *XPB*, *XPC*, and others), present with hypersensitivity to UV light and a high cancer incidence, similar to that seen in XP patients[141]. Interestingly, mouse models of CS, which are caused by mutations in the *NER* genes *ERCC6* and *ERCC8*, also present with accelerated aging and a predisposition to cancer[142].

(9) Mouse models of NBS have hypomorphic mutations in *Nbn1*, and null mutations of *Nbn* are embryonically lethal[143]. Mice harboring hypomorphic mutations in *Nbn* are viable, but they do not demonstrate any neurological phenotypes as that seen in the human NBS patients[144]. The cerebellum of *Nbn* mice has agenesis and decreased proliferation of neuronal progenitor cells accompanied by marked death of cerebellar neurons[145]. Specific deletion of *Nbn* in the mouse CNS ($Nbn^{CNS\text{-}del}$) leads to growth retardation and early onset of cataracts[146], as well as microcephaly, decreased white matter integrity, retina and astrocyte functionality, recapitulating the microcephaly seen in human patients with NBS[147-149].

DIFFERENCES IN THE DNA DAMAGE AND REPAIR RESPONSE BETWEEN HUMAN AND MOUSE NEURONS AND ASTROCYTES

It is interesting that many mouse models of DNA damage repair do not faithfully recapitulate the neurological symptoms seen in their human counterparts, suggesting that there are inherent differences in DNA damage repair between mouse and human neurons. Indeed, a recent study comparing mouse and human neurons identified distinct differences in their response to different forms of DNA damage[150]. Human and mouse neurons treated with identical doses of the DNA damaging agent camptothecin (CPT) for the same period of time demonstrated markedly different alterations in the nuclei of degenerating neurons. CPT-treated differentiated human neurons showed homogeneous and uniform chromatin condensation within the nucleus but did not form discrete round chromatin clumps or crescentic marginations at the nuclear envelope nor form discrete round chromatin clumps at the nuclear envelope as would be seen during neuronal apoptosis; instead, they demonstrated signs of pyknosis. In contrast, mouse neurons demonstrated signs of apoptosis which was demonstrated consistently regardless of where neurons were harvested in the mouse brain. Mouse neurons underwent apoptosis through activation of caspase-3, while human neurons only had mild activation of caspase-3 but instead showed robust activation of caspase-6. Interrogation of the mitochondria cell death pathway also demonstrated different response rates between human and mouse neurons. Mouse neurons had early activation of Bax while Noxa levels remained at baseline, and Puma levels also had an early spike in response to CPT. In contrast, human neurons had a much later spike of Bax levels, while Noxa and Puma levels exhibited a significant and progressive increase over the course of many hours throughout the treatment course[150]. Finally, an investigation of the individual components of the DDR pathway in mouse and human neurons during CPT treatment demonstrated that mouse neurons did not mount a robust activation of the MRN complex, which senses DSBs caused by CPT, while human neurons mounted a rapid activation of MRN. Human neurons showed sustained activation of ATR, p53 and p73, while mouse neurons showed rapid suppression of ATR and had sustained activation of p53 and p73[150].

Another study identified differences in the response of mouse and human astrocytes to oxidative stress, hypoxia, inflammatory cytokine treatment, and simulated viral infections[151]. This study helps shed light on why many mouse models of neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, and Huntington's disease often have milder phenotypes compared to human patients, possibly owing to the inherent increased resilience of mouse astrocytes to the effects of oxidative stress. The authors also showed that mouse astrocytes activated a pro-growth program in response to hypoxia but not in human astrocytes, possibly explaining the greater functional recovery observed in mouse models of ischemic stroke compared to human stroke patients. Taken together, these studies demonstrate differences in the ways that different populations of mouse and human brain cells process DNA damage and other forms of cellular stress and insult, and further address the potential limitations in interpreting studies performed using animal models of DNA damage and neurological diseases.

CONCLUSION

In summary, the ability of human cells to respond effectively to daily endogenous and exogenous sources of DNA damage ensures longevity and health. As we continue to uncover a further mechanistic understanding of these inherited syndromes, the hope is to be able to discover targeted therapies that will effectively reverse the devastating effects of these diseases and improve the quality of life and survival for these patients.

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The author contributed solely to the article.

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