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Dysregulation of the DNA repair-immune axis: Targeted therapeutic strategies for autoimmune diseases (Review)

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Abstract. DNA damage and repair mechanisms are crucial for maintaining genomic stability, and their dysregulation is closely linked to the complex pathogenesis of autoimmune diseases. The present review systematically describes the types of DNA damage, key repair pathways, their regulatory networks, and the multidimensional interactions between DNA repair and the immune system. Furthermore, it delves into how defective DNA repair drives the development of autoimmune disorders such as systemic lupus erythematosus and rheumatoid arthritis through mechanisms encompassing cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway activation, self-antigen release and breakdown of immune tolerance. Oxidative stress-induced DNA damage, mutations in repair genes and aberrant accumulation of cytosolic DNA are key triggers of autoimmune responses. In addition, DNA repair proteins indirectly influence disease progression by modulating immune cell functions, including T-cell homeostasis and macrophage polarization. The present review further summarizes the therapeutic potential and challenges of targeting DNA damage response pathways, including via poly adenosine diphosphate ribose polymerase inhibitors and cGAS-STING axis regulation, as demonstrated in pre-clinical models. Future research leveraging multi-omics and innovative delivery systems will be crucial for translating these discoveries into effective, personalized therapies. The present review advances the development of personalized precision medicine and provides a solid theoretical foundation for developing novel treatment strategies.

Contents

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Abbreviations: ATM/ATR, ataxia telangiectasia mutated/ataxia telangiectasia and Rad3 related; BER, base excision repair; cGAS, cyclic GMP-AMP synthase; cfDNA, cell-free DNA; DC, dendritic cell; DDR, DNA damage response; DSB, double-strand break; HR, homologous recombination; IFN, interferon; MS, multiple sclerosis; mtDNA, mitochondrial DNA; NER, nucleotide excision repair; NHEJ, non-homologous end joining; NK cell, natural killer cell; OGG1, 8-oxoguanine DNA glycosylase 1; PARP, poly adenosine diphosphate ribose polymerase; PD-L1, programmed death ligand 1; RA, rheumatoid arthritis; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSB, single-strand break; TREX1, three prime repair exonuclease 1; Th, T helper; Treg, regulatory T cell

Key words: DNA damage and repair, autoimmune diseases, immune homeostasis dysregulation, cGAS-STING pathway, targeted therapy

1. Introduction

DNA damage and repair, as the core mechanism for maintaining genomic stability, are critical for safeguarding the integrity of genetic material and sustaining cellular homeostasis and organismal health. DNA damage can be caused by a combination of endogenous factors (such as oxidative stress or replication errors) or exogenous factors (such as ultraviolet rays or chemical toxins) (1,2), with major types of DNA damage including single-strand breaks (SSBs), double-strand breaks (DSBs), base modifications, cross-links and large insertions/deletions (3). Failure to promptly repair these damages may lead to genomic instability and abnormal cellular function, and may even drive pathological processes such as cancer, neurodegenerative diseases and autoimmune diseases (1,4-6).

In response to damage, cells have evolved several repair mechanisms. Base excision repair (BER) specifically recognizes and excises oxidatively damaged bases (such as 8-oxoguanine) through DNA glycosylases [such as 8-oxoguanine DNA glycosylase 1 (OGG1)] (7,8). Nucleotide excision repair (NER) removes large-scale damage. Homologous recombination (HR) and non-homologous end joining (NHEJ) repair DSB through precision repair or direct joining, respectively. On one hand, RNA molecules can directly participate in repair regulation, with their own chemical modifications (such as 5-methylcytosine) can promote repair efficiency; furthermore, transcripts or damage-associated RNAs can serve as repair templates, guiding precise repair (9,10). On the other hand, post-translational modifications of the repair proteins themselves, such as phosphorylation and acetylation, precisely control their localization, activity and function, forming the dynamic regulatory core of the repair network (11). Notably, DNA repair defects are not only closely associated with genomic instability and cancer development but also contribute to immune system abnormalities. For instance, defects in the KU complex, a core component of the DNA-dependent protein kinase holoenzyme, can trigger autoimmune response linked to T cell senescence (12,13). Therefore, the present review summarizes the research on the mechanism of DNA repair-immune axis dysregulation, the development of related diseases and the future direction of targeted therapy.

Autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), are fundamentally characterized by the immune system losing tolerance to self-antigens, leading to the production of autoantibodies and/or autoreactive T cells, thereby causing chronic inflammation and tissue damage in specific organs or throughout multiple systems of the body. Their pathogenesis involves genetic predisposition, epigenetic regulatory abnormalities and immune homeostasis imbalances (14-16). Previous studies have confirmed that DNA damage and repair abnormalities exacerbate autoimmune disease progression through multiple mechanisms. Uncleared extracellular DNA (for example, microsomal-bound DNA) can be recognized as a danger signal activating the cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) pathway and promoting type I interferon secretion to drive lupus-like autoimmunity (17-19). Oxidative stress modulates DNA methylation to affect immune cell differentiation, further promoting the activation of autoreactive T cell (15,20). Meanwhile, sustained accumulation of DNA damage can trigger chronic low-grade inflammation, accelerating autoimmune processes (21).

Despite significant progress in the field, key challenges remain. First, the causal relationship between DNA damage and autoimmunity has not been fully elucidated. Whether oxidative damage is the initial trigger or a secondary consequence of chronic inflammation requires verification using dynamic spatiotemporal tracking techniques (22). Second, the regulation of immune cell repair pathways exhibits high heterogeneity. For instance, single-cell RNA sequencing analysis have revealed that cGAS-STING pathway serves a unique role in maintaining the antitumor functions of $CD8^+$ T cells (23), suggesting that different immune cells may differentially regulate DNA damage response (DDR) pathways through mechanisms such as epigenetic reprogramming. Third, the immune checkpoint protein programmed death ligand 1 (PD-L1) serves a complex role in the cross-regulation between the DDR and innate immunity. On one hand, PD-L1 expression is induced by DNA damage signals [such as the ataxia telangiectasia mutated (ATM)/ataxia telangiectasia and Rad3 related (ATR) pathways] and may affect genomic stability by, for example, stabilizing key repair complexes (24,25). On the other hand, PD-L1 negatively regulates the cGAS-STING pathway, providing a novel direction for immune cell-specific targeting strategies (26).

Novel therapeutic strategies targeting the dysregulation of the DNA repair-immune axis have shown promising potential. STING agonists combined with poly adenosine diphosphate ribose polymerase (PARP) inhibitors synergistically enhance DNA damage-induced immunogenic death while remodeling the immune microenvironment through epigenetic regulation (27,28). Nanomedicines targeting the cGAS-STING-TANK-binding kinase 1 (TBK1) axis selectively inhibit autoreactive T cells, achieving remission in experimental autoimmune encephalomyelitis models (29,30). Radiotherapy activates the cGAS-STING pathway by inducing DNA damage and releasing it into the cytoplasm, and preclinical studies have confirmed that this key antitumor immune activation mechanism can significantly enhance the efficacy of immune checkpoint inhibitors (31-33). DNA damage markers provide assessment tools, while repair pathway modulation demonstrates therapeutic potential in preclinical models (34-37). The present review systematically summarizes the central role of the DDR in autoimmunity and constructs a conceptual framework for targeting the DDR-immune axis, providing a theoretical basis for the development of novel therapeutic strategies.

2. Trajectory of research on DNA damage and repair

The trajectory of research on DNA damage and repair in autoimmune diseases clearly demonstrates an evolutionary path from phenomenological association to mechanistic dissection, and ultimately towards targeted therapy, as presented in Fig. 1. Early studies (1960s-1990s) established a preliminary link between DNA repair defects and human diseases by observing syndromes such as xeroderma pigmentosum, and also revealed evidence of genomic instability in patients with SLE and other autoimmune conditions (38-41).

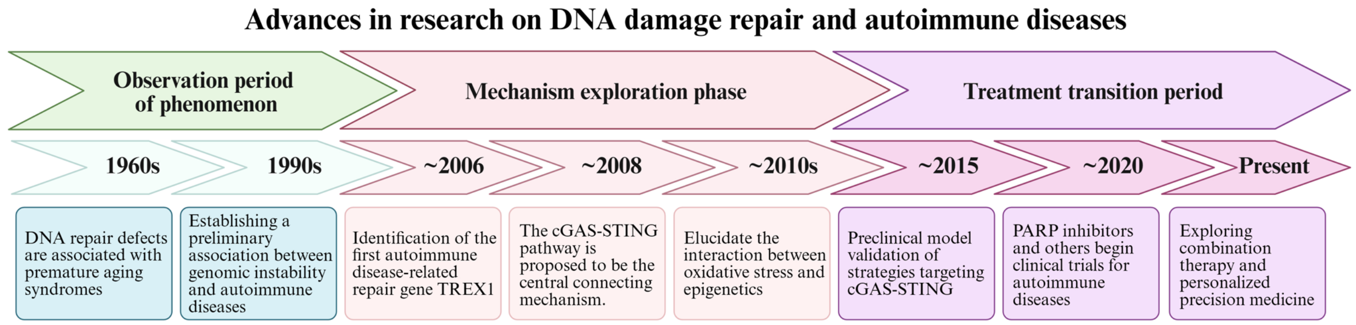

Figure 1. Timeline of key advances in research on DNA damage repair and autoimmune diseases. This figure outlines the major milestones in understanding the link between impaired DNA repair and autoimmune pathogenesis. The timeline begins in the 1960s with the observation that DNA repair defects are associated with premature aging syndromes. In the 1990s, a preliminary association between genomic instability and autoimmunity was established. Landmark discoveries include the identification of the first autoimmune-related repair gene TREX1 in 2006, the proposal of the cGAS-STING pathway as a central connecting mechanism in 2008, and the elucidation of interactions between oxidative stress and epigenetics in the 2010s. More recent advances include preclinical validation of cGAS-STING-targeted strategies (2015), the initiation of clinical trials using PARP inhibitors for autoimmune diseases (2020), and current explorations into combination therapies and personalized precision medicine. TREX1, three prime repair exonuclease 1; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; PARP, poly adenosine diphosphate ribose polymerase.

Entering the 21st century, mechanistic research achieved a breakthrough in progress. The seminal discovery in 2006 that loss-of-function mutations in the three prime repair exonuclease 1 (TREX1) genes cause a severe type I interferonopathy, linked aberrant accumulation of cytoplasmic DNA to autoimmunity for the first time (Fig. 1) (42). The period from 2008 to 2013 yielded a pivotal discovery with the identification of the cGAS-STING pathway as the cytosolic DNA sensor, which provided the core molecular explanation for this association (Fig. 1) (43). This established the central paradigm that unrepaired DNA triggers cGAS-STING activation, initiating a cascade of events, a type I interferon response that drives autoimmunity (44). Concurrent research also revealed the synergistic role of oxidative damage and epigenetic reprogramming in disrupting immune homeostasis (15,20).

In recent years, research has entered a translational phase. Preclinical models have demonstrated the potential of targeting the cGAS-STING axis and enhancing deoxyribonuclease 1-like 3 (DNase1L3) activity for the treatment of autoimmune diseases (19,45,46). In the mouse models of hereditary and induced lupus erythematosus, a bifunctional enzyme (DNASE1/dnase1l3) was found to significantly prevent the onset and death in mice with autoimmune diseases, which directly proved the therapeutic potential of enhancing the activity of DNase1L3 (19). In addition, a class of covalent small molecule inhibitors (such as C-178 and C-176) can directly target and inhibit sting protein to block type I interferon response, which provides key preclinical validation for the treatment of autoimmune diseases through drug inhibition of cGAS-STING pathway (45). Furthermore, the exploration of cell-free DNA (cfDNA) as a biomarker for precision medicine strategies marks the advancement of the field towards a new era of individualized targeted therapy (47,48).

3. Basic theory and progress of DNA damage and repair

DNA damage is a major source of genomic instability, comprising endogenous damage [including replication errors and reactive oxygen species (ROS)-induced oxidative damage] and exogenous damage (including UV radiation and chemical mutagens) (49). At the molecular level, damage includes SSBs, DSBs, base modifications, cross-links and large insertions/deletions (3) (Table I). These damages are handled by specific repair pathways. For example, BER mainly repairs oxidative base damage, while HR or NHEJ specifically deals with DSBs. It is worth noting that these repair mechanisms are closely related to autoimmune diseases. For example, BER defects are related to SLE and RA, while the elimination of cytoplasmic DNA is closely related to autoimmune syndrome characterized by type I interferon reaction, which systematically explains the potential pathways of DNA damage and repair imbalance involved in autoimmune pathogenesis at the molecular level. Eukaryotes maintain genome stability through five pathways: BER, NER, mismatch repair, HR and NHEJ (3). Notably, ultraviolet light-induced pyrimidine dimers are repaired primarily via the NER, whereas radiation-induced DSBs are processed by either HR or NHEJ (50), with distinct spatiotemporal specificities: HR utilizes sister chromatids for DSB repair exclusively in the S/G_2 phase, whereas NHEJ directly ligates breaks throughout the cell cycle (11,51) (Fig. 2). The precise execution of these pathways is regulated by multi-level coordination: Post-translational modifications precisely regulate repair (52); RNA-mediated mechanisms have expanded the traditional paradigms (for example, human DNA polymerase θ can utilize RNA templates to direct the repair of DSB) (10,53); and tissue-specific differences markedly influence pathway choice (for example, neurons prefer NHEJ due to absent HR factors, including BRCA1/2) (11,54). Endogenous DNA damage is closely linked to the metabolic microenvironment. For instance, ROS generated during oxidative stress induce base lesions that are predominantly repaired by the BER pathway. Conversely, replication stress can lead to stalled replication forks, whose restart and stabilization depend on HR (Fig. 2) (55-57). The chromatin status affects damage susceptibility and repair. Transcription factor-binding regions are more vulnerable, while compact heterochromatin inherently impedes the access of repair machinery (58). Separately, impaired DNA repair itself is a direct driver of disease. For example, FANCD2/FANCI-associated nuclease 1 deletion in

Table I. Types of DNA damage and corresponding repair pathways.

Type of damage	Primary repair pathway	Key proteins/factors	Associated autoimmune diseases	(Refs.)
Oxidative base damage (e.g., 8-oxoguanine)	BER	OGG1, XRCC1	SLE, RA, SS	(85,124,125,142,149)
DSB	HR	BRCA1, BRCA2, Rad51	Cancer-related autoimmunity	(178)
	NHEJ	KU70/80, DNA-PKcs	SLE (T cell dysregulation)	(12,13)
SSB	SSBR	PARP1, XRCC1	RA, SS, SLE	(39,127,128,140)
Bulky lesions (e.g., pyrimidine dimers)	NER	XPC, ERCC1	Cutaneous autoimmune phenotypes	(38,40,115,116)
Mismatches/insertions-deletions	MMR	MSH2, MLH1	Autoimmunity in Lynch syndrome	(5)
Cytosolic DNA accumulation	DNA degradation (Nucleases)	TREX1, DNase1L3	SLE, Aicardi-Goutières Syndrome	(17,42,45,46,130)

BER, base excision repair; DSB, double-strand break; HR, homologous recombination; NER, nucleotide excision repair; NHEJ, non-homologous end joining; OGG1, 8-oxoguanine DNA glycosylase 1; PARP, poly adenosine diphosphate ribose polymerase; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSB, single-strand break; TREX1, three prime repair exonuclease 1; MMR, mismatch repair; SSBR, single-strand break repair; PKcs, DNA-dependent protein kinase catalytic subunit; XRCC1, X-ray repair cross complementing protein 1; DNase1L3, deoxyribonuclease 1-like 3.

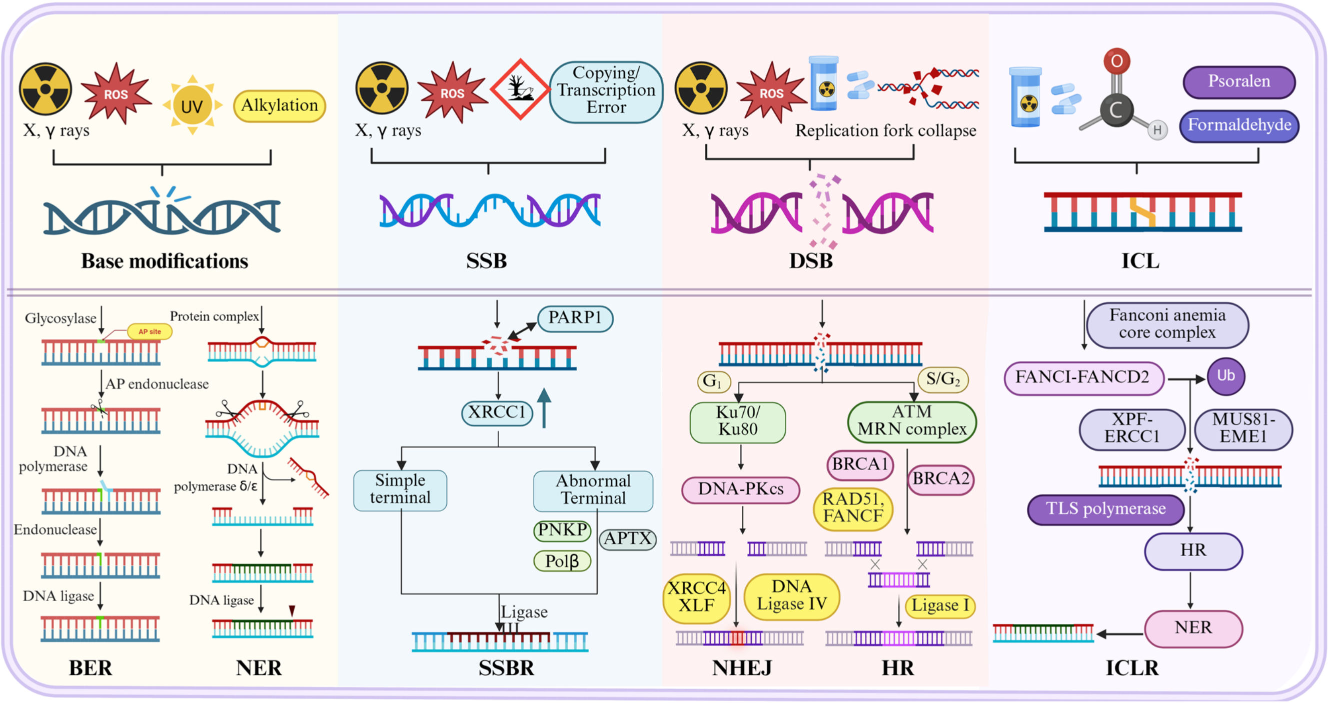

Figure 2. A schematic network of major DNA damage response and repair pathways. A summary of the key pathways responsible for repairing different types of DNA lesions. At the top, base modifications and SSBs are primarily repaired through the BER pathway, initiated by glycosylases and involving endonucleases, DNA polymerases and DNA ligases. The middle section outlines the main repair pathways for various DNA damages, including BER, NER, SSBR, NHEJ, HR and ICLR. For more severe damage, such as DNA DSBs and ICLs, the lower portion highlights the central proteins and complexes involved. For example, the Ku70/Ku80 complex in NHEJ, the BRCA1/2 and RAD51 proteins in HR, and the Fanconi anemia core complex in ICLR. Key molecules and steps are indicated throughout, illustrating the coordination of repair factors according to the specific lesion. SSB, single-strand break; BER, base excision repair; NER, nucleotide excision repair; SSBR, single-strand break repair; NHEJ, non-homologous end joining; HR, homologous recombination; ICLR, interstrand cross-link repair; DSB, double-strand break; ICL, interstrand cross-link; ROS, reactive oxygen species; PARP, poly adenosine diphosphate ribose polymerase; XRCC1, X-ray repair cross complementing protein 1; PNKP, polynucleotide kinase 3'-phosphatase; APTX, Aprataxin; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; XLF, XRCC4-like factor; ERCC1, excision repair cross-complementation group 1.

chronic kidney disease leads to tubular DNA damage accumulation and fibrosis, highlighting how a deficiency in a specific repair factor can cause pathogenic microenvironment-repair imbalance (59,60).

The DDR network coordinates repair through dynamic signaling. Core sensors ATM/ATR kinases activate phosphorylation cascades upon detecting DSBs or replication stress (61). Repair proteins form dynamic foci [such as phosphorylated histone H2AX (γH2AX)] whose composition and function changes with aging, increasing error-prone repair (Fig. 2) (62). Epigenetic regulation via chromatin remodeling complexes promotes repair factor recruitment (58). Beyond chromatin, a RNA-centric regulatory layer has emerged, where RNA-binding proteins and long non-coding RNAs are increasingly recognized for their role in fine-tuning DSB repair pathway choice and efficiency (63,64). Critically, DNA damage repair is intricately linked to cell fate decisions. Unfinished repair activates the p53 pathway to induce cell cycle arrest or apoptosis (65), while adult stem cells employ continuous repair for rapid damage response during migration (66). Damage-released DNA fragments activate the cGAS-STING pathway, converting genomic instability into antitumor immune responses, and the circadian protein neuronal PAS domain protein 2 enhances HR repair by stabilizing H2AX mRNA, suggesting circadian regulation of repair efficiency (67-69). These mechanisms collectively establish the pivotal role of DNA repair in cellular homeostasis.

Technological innovations have markedly advanced this field. High-resolution damage mapping achieves single-nucleotide level precision (70). In addition, CRISPR-based functional screening reveals cross-regulation between DNA repair and MAPK/ERK signaling (71,72). Furthermore, stochastic kinetic models quantify the intrinsic efficiency limitations of repair pathways, such as the competition between repair and lesion bypass in transcription-coupled repair (73). Additionally, emerging technologies such as single-cell sequencing and nanoradiostatic sensitizers are overcoming traditional research bottlenecks. Single-cell sequencing resolves the critical issue of cellular heterogeneity by mapping distinct DNA damage responses and repair capacities across individual cells within complex tissues. Nanoradiostatic sensitizers overcome therapeutic resistance by irreversibly disrupting key DNA repair processes, thereby transforming reparable lesions into lethal and immunogenic damage (74). These tools not only deepen the understanding of basic repair mechanisms but also provide novel strategies for translating repair-related research into clinical applications.

4. Interaction of DNA damage and repair with the immune system

The interplay between the DDR and immune system functionality is pivotal in maintaining immune homeostasis, while the dysregulation of the DNA repair-immune axis contributes to autoimmune diseases, chronic inflammation and immunosenescence (75,76). This section explores how DNA repair defects across immune cell lineages drive autoimmune pathogenesis by disrupting immune homeostasis (Fig. 3).

T cells. T cells are the core of adaptive immunity, and T cell function is markedly impacted by the accumulation of DNA damage. Studies have demonstrated that the dynamic balance between DNA damage and repair not only regulates T cell activation, differentiation and homeostasis maintenance (77), but is also closely associated with autoimmune diseases and immune senescence (78-80). During aging, T cells develop genomic instability due to decreased DNA repair capacity, manifesting as reduced proliferative potential and weakened effector functions, ultimately leading to immune senescence (81,82).

In autoimmune conditions, activated T cells accumulate ROS-induced oxidative DNA damage, creating a vicious cycle that further exacerbates inflammatory responses. In autoimmune hepatitis, for instance, $CD4^+$ T cells exhibit markedly elevated 8-oxoguanine levels, which are positively associated with hepatic inflammation severity (12). Notably, regulatory T cells (Tregs), critical for immune tolerance maintenance, also exhibit DNA repair capacity-dependent function. Defects in BER pathway components in Tregs impair Foxp3 stability, driving their conversion to pro-inflammatory T helper 17 (Th17) cells and thereby disrupting autoimmune homeostasis (83-85) (Fig. 3).

As pivotal cytotoxic effectors, $CD8^+$ T cells require stringent genomic stability to maintain their proliferative capacity, survival and effector functions. In the inflammatory milieu of autoimmune diseases, $CD8^+$ T cells are subjected to sustained oxidative and replicative stress, leading to the accumulation of DNA damage, including oxidized bases (such as 8-oxoguanine) and DSBs (81,86). This damage accrual is not merely a passive consequence but an active driver of dysfunction. Mechanistically, unrepaired DNA damage in $CD8^+$ T cells can trigger cell-intrinsic signaling cascades that promote a state of functional exhaustion or impaired differentiation. The cytoplasmic accumulation of nuclear or mitochondrial DNA (mtDNA) fragments, resulting from defective repair or mitochondrial distress, activates the cGAS-STING pathway (23,87). While this pathway is crucial for antitumor and anti-viral immunity, its chronic activation in autoimmune contexts drives $CD8^+$ T cells toward an exhausted phenotype, characterized by increased expression of inhibitory receptors (such as programmed death 1 and T cell immunoglobulin and mucin domain-containing protein 3), impaired cytokine production [including interferon (IFN)-γ and TNF-α production] and reduced cytotoxic potential (23,83,87). This exhaustion-like state compromises their ability to clear aberrant self-reactive cells or regulate immune responses, thereby contributing to disease persistence. Furthermore, DDR deficiencies can directly alter $CD8^+$ T cell metabolism and epigenetic programming. For instance, persistent DSB signaling can rewire cellular metabolism toward a suppressive state and enforce epigenetic changes that stabilize the exhausted transcriptional program (88). In patients with SLE and RA, $CD8^+$ T cells often exhibit features of senescence and exhaustion, which are associated with disease activity and may be rooted in unresolved genomic stress (81,89).

DNA repair regulates macrophage function. As important effector cells of innate immunity, the functional state of macrophages (for example, pro-inflammatory M1-type or anti-inflammatory M2-type polarization) is closely related to the dynamic balance of DNA damage and repair mechanisms. During chronic inflammation and aging, the sustained DDR induces macrophage conversion to a pro-inflammatory phenotype (M1), and promotes the formation of an inflammatory

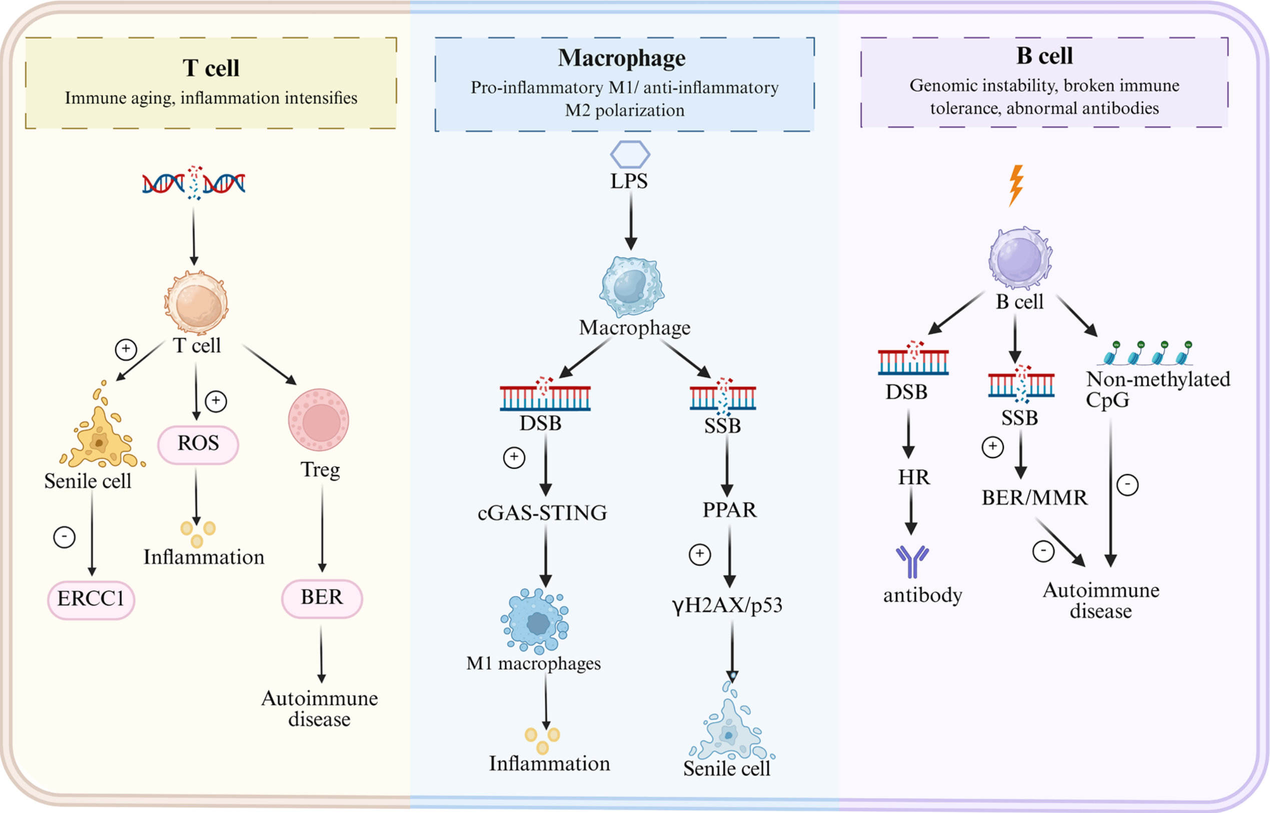

Figure 3. Interaction between DNA damage and repair and different immune cells. This schematic illustrates how defective DNA damage response in major immune cell types contributes to loss of tolerance and autoimmunity. In T cells, elevated ROS and deficiencies in BER promote immune aging and inflammation, potentially driving T cells toward an autoimmune phenotype. In macrophages, external triggers such as LPS induce DNA DSBs, activating the cGAS-STING pathway and downstream p53 signaling, which skews polarization toward a pro-inflammatory M1 state. In B cells, genomic instability due to impaired repair pathways (e.g., BER, MMR) and unrepaired DSBs can break immune tolerance, leading to the production of abnormal antibodies. Together, these cell-specific disruptions in DNA repair create a pro-inflammatory, self-reactive immune environment that underlies autoimmune disease development. ROS, reactive oxygen species; BER, base excision repair; DSB, double-strand break; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; MMR, mismatch repair; Treg, regulatory T cells; ERCC1, excision repair cross-complementation group 1; SSB, single-strand break; PPAR, peroxisome proliferator-activated receptor; γH2AX, phosphorylated histone H2AX; HR, homologous recombination.

microenvironment through the secretion of pro-inflammatory factors such as IL-1β and TNF-α (Fig. 3) (90). Genotoxic stresses in the microenvironment (including ROS, chemotherapeutic agents or radiation) can induce DNA damage in macrophages, which subsequently regulates their immune phenotype and function through activation of the cGAS-STING pathway or PARP-dependent repair pathways (91). Studies have demonstrated that mtDNA release drives M1 polarization of macrophages via the cGAS-STING pathway, while PARP-1 overactivation promotes inflammatory factor production by modulating NF-κB signaling (92,93). However, long-term DNA damage accumulation also leads to macrophage dysfunction, characterized by impaired phagocytic capacity and compromised antigen presentation, which contributes to tumor progression or senescence-associated inflammation (94,95) (Fig. 3). In the tumor microenvironment, macrophages frequently exhibiting DNA damage promote immune escape by secreting immunosuppressive factors such as IL-10 and TGF-β, whereas during aging, persistent DNA damage in macrophages alters their secretory phenotype, fostering chronic inflammatory conditions in tissues (Fig. 3). These findings reveal the central role of the DNA damage repair balance in regulating macrophage function, providing novel perspectives for the treatment of related diseases.

B cells. B cell activation and antibody production are strictly dependent on the maintenance of genomic stability (Fig. 3). The maintenance of B cell function depends on some specific DNA repair pathways, such as BER and HR. Impairment here markedly increases genomic instability in B cells, causing errors in somatic hypermutation and class switch recombination processes, ultimately resulting in aberrant antibody production or breakdown of immune tolerance (96). Toll-like receptor 9 (TLR9) recognizes pathogen DNA to drive B cell activation (97,98); however, the aberrant accumulation of self-nucleic acids due to nuclease deficiencies (for example, in TREX1) can be misrecognized by intracellular sensors such as TLR9 or cGAS-STING, driving inappropriate B cell activation and a type I interferon response that is central to the pathogenesis of systemic lupus erythematosus (99). In the tumor microenvironment, B cells mediate antitumor immunity via antigen presentation; however, their function is modulated by damage-associated molecular patterns (DAMPs) released from tumor cells. These DAMPs alter B-cell activation status, antigen presentation efficiency and costimulatory molecule expression (100). Notably, emerging evidence suggests that in pathological contexts such as chronic infection or cancer, persistent DNA damage stress within the tumor microenvironment can skew B cell differentiation. This may contribute to the expansion of regulatory B cells (Bregs) or otherwise dysfunctional B cells that promote immune escape by inducing immunosuppressive factor secretion (including IL-10 and TGF-β secretion) (101). A recent study has further revealed that specific DNA repair pathways, such as NHEJ, serve essential roles in B cell antibody diversity generation and affinity maturation (102). For example, during early development, NHEJ facilitates V(D)J recombination to assemble the primary B cell receptor repertoire; following activation, it ensures the fidelity of class-switch recombination to alter antibody class (102). This provides novel perspectives for understanding the central position of DNA repair mechanisms in adaptive immunity.

Innate immune cells. Innate immune cells [such as natural killer (NK) cells and dendritic cells] can sense DNA damage signals through nucleic acid sensors. For example, tumor-derived cfDNA or self-DNA released from cells can be taken up by antigen-presenting cells such as dendritic cells (DCs) (33). Activation of the cGAS-STING pathway in these DCs promotes their maturation and the production of cytokines (for example, type I interferons), which, in turn, can enhance NK cell activation and drive adaptive antitumor immunity (33,91,103,104). However, chronic DNA damage may lead to hyperactivation of intrinsic immunity, triggering autoinflammation or tissue damage (105). In addition, certain proteins involved in the DNA damage response exhibit immunomodulatory functions. For example, DNA repair factors (such as Growth arrest and DNA damage-inducible 45 family of proteins) have been shown to be involved in DNA repair and to regulate inflammatory responses in various cell types, playing an important immunoregulatory role in a variety of inflammatory and autoimmune diseases (106,107).

Regulation of the immune response by DNA damage and repair. DNA damage drives inflammatory responses through multiple mechanisms. Acute damage (such as that caused by infection or radiotherapy) activates both the cGAS-STING and NF-κB pathways, promoting the release of pro-inflammatory factors such as IL-6 and TNF-α, thereby enhancing antitumor or antiviral immunity (94,103). Specifically, cGAS recognizes cytoplasmic DNA to form dimers that catalyze cyclic GMP-AMP production, subsequently activating the STING protein and initiating type I interferon responses (108). However, chronic damage (such as that caused by aging or metabolic stress) leads to a persistent inflammatory microenvironment that promotes tumor progression or aging-related diseases (90,109,110). For instance, senescent cells mainly create a persistent pro-inflammatory microenvironment via the senescence-associated secretory phenotype, which involves the secretion of a large number of chemokines (such as CCL2, CXCL1 and CXCL8). These factors actively recruit immune cells such as monocytes and neutrophils. These cells, together with the senescent cells themselves, release various inflammatory mediators, including IL-1, IL-6 and MMPs, thereby establishing a chronic low-grade inflammatory state (90,111). In addition, previous foundational studies, along with more recent work, have shown that DNA repair enzymes (such as mutT homologs) can maintain genomic stability by preventing the incorporation of oxidatively damaged nucleotides into DNA, offering a novel perspective for treating autoimmune diseases by targeting genomic instability (100,112).

DNA damage and immune senescence. DNA damage is a key driver of immune senescence, a process characterized by T cell dysfunction and chronic inflammation (81,113). Senescent T cells exhibit telomere shortening, mitochondrial dysfunction and sustained activation of the DDR signaling pathway (81,114). Specifically, telomeres are shortened by 50-100 base pairs annually on average, leading to upregulated expression of the cell cycle arrest-related protein p21. Concurrently, the mitochondrial membrane potential decreases, ATP production diminishes and mtDNA release occurs (114). Impaired DNA repair capacity, exemplified by excision repair cross-complementation group 1 (ERCC1) deficiency, accelerates hematopoietic senescence and compromises immune cell reconstitution (115,116). Hematopoietic stem cells with ERCC1 deficiency exhibit markedly reduced self-renewal capacity and a tendency to differentiate into myeloid cells rather than lymphoid cells, which disrupts immune homeostasis (116,117). Notably, an elevated frequency of mutations in DNA repair genes in the elderly population is associated with increased infiltration of $CD8^+$ T cells and M1 macrophages, suggesting a complex association between the DDR and age-related immune remodeling (118). The frequency of somatic mutations in repair genes (such as TP53 and ATM) in peripheral blood cells of individuals >70 years of age is markedly higher than that of young adults (119,120). This genomic instability, combined with inflammatory immune cell infiltration, constitutes the molecular foundation of immune senescence. Interventional strategies, such as senolytics (senescent cell-targeting agents), delay immune senescence via senescent cell elimination or DNA repair enhancement ('genoprotection') (81,95,121). For instance, the combination of dasatinib and quercetin specifically clears senescent immune cells and restores thymic function (122).

5. In-depth study of DNA damage and repair and specific autoimmune diseases

The accumulation of DNA damage and deficiencies in repair pathways are now recognized as fundamental drivers in the pathogenesis of various autoimmune diseases. While the clinical manifestations and target organs differ, a common thread linking conditions such as Sjögren's syndrome (SS), RA, SLE and multiple sclerosis (MS) is the breakdown of immune tolerance triggered by genomic instability (42,123,124), The main core mechanisms involved in various autoimmune diseases include the sustained accumulation of oxidative DNA damage, functional defects in specific repair genes, resulting abnormal accumulation of cytoplasmic DNA, and ultimately excessive type I interference response and chronic inflammation triggered by innate immune sensing pathways such as cGAS STING. These links are intertwined, forming a 'damage inflammation' cycle that collectively destroys immune tolerance (Fig. 4).

SS

Clinical evidence of SS. SS is a chronic autoimmune disease characterized by lymphocytic infiltration of exocrine glands

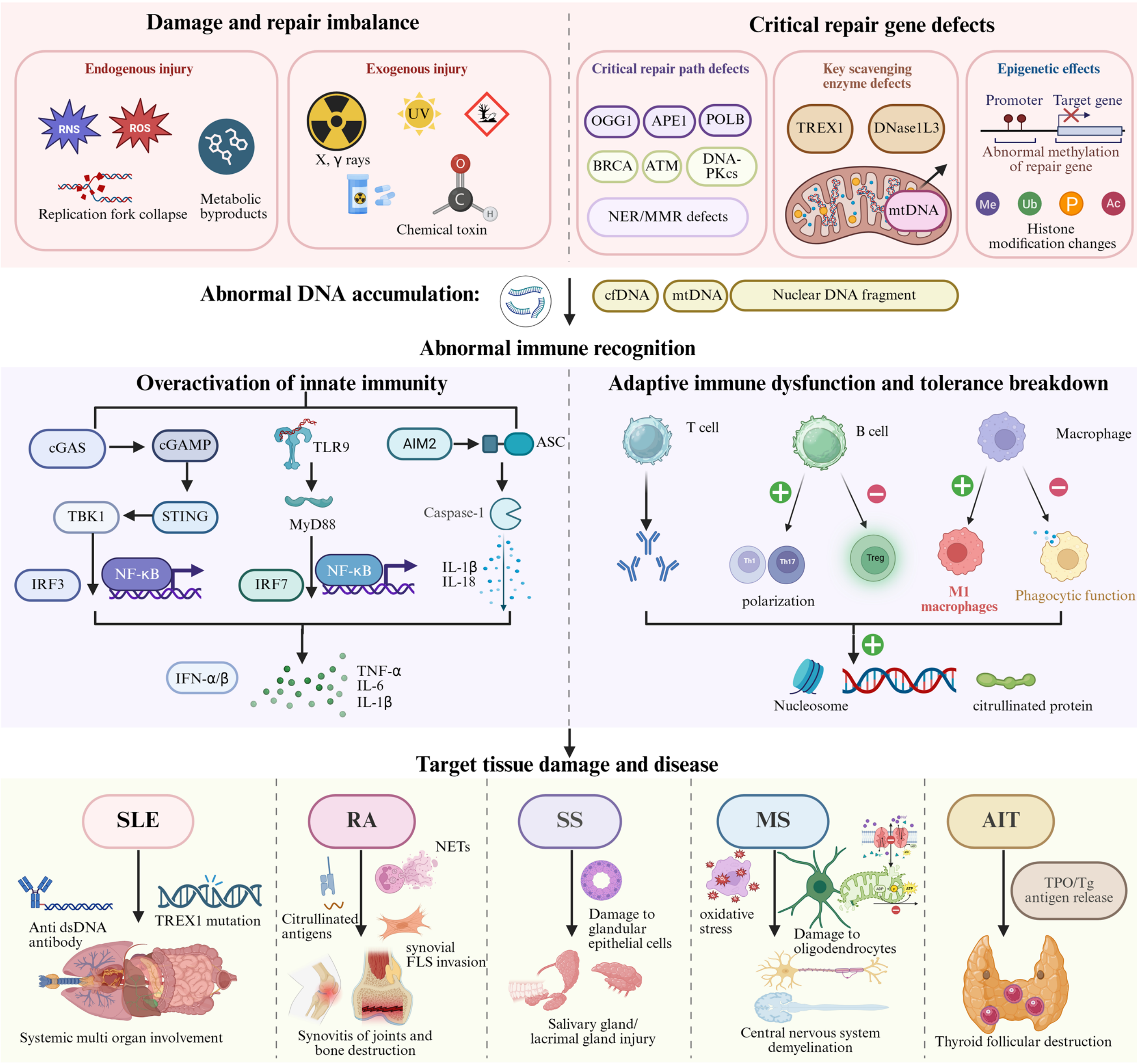

Figure 4. Schematic representation of the pathogenic axis from DNA damage and repair imbalance to autoimmune disease development. This figure illustrates the conceptual framework through which dysregulation of the DDR triggers and perpetuates autoimmunity. The cascade begins with endogenous (for example, replication stress, mitochondrial dysfunction) and exogenous (for example, radiation, chemical toxins) sources of DNA damage. Inefficient repair due to defects in critical repair pathways (involving proteins such as OGG1, APE1 and POLB), key scavenging enzymes (such as, TREX1, DNase1L3), or epigenetic dysregulation leads to the abnormal accumulation of genomic and mtDNA in the cytoplasm. This misplaced DNA is sensed as a 'danger signal' by innate immune sensors, primarily the cGAS-STING and TLR9 pathways. Their overactivation initiates a potent IFN-I and pro-inflammatory cytokine response (e.g., via NF-κB), creating a chronic inflammatory milieu. This environment, characterized by IFN-I, IL-6, TNF-α, and others, disrupts immune homeostasis by promoting the activation of autoreactive T and B cells, impairing Treg function, and driving macrophage polarization towards a pro-inflammatory (M1) phenotype. The breakdown of immune tolerance ultimately manifests as organ-specific or systemic autoimmune diseases, including SLE, RA, SS and MS. In MS, oligodendrocyte damage is exacerbated not only by oxidative stress and direct DNA injury but also by associated mitochondrial dysfunction, including diminished membrane potential and impaired ATP production, which further compromises cellular integrity and repair capacity. Solid arrows indicate direct promoting actions or sequential steps; dashed arrows represent contributions to the inflammatory microenvironment or disease outcomes. DDR, DNA damage response; BER, base excision repair; NER, nucleotide excision repair; NHEJ, non-homologous end joining; HR, homologous recombination; TREX1, three prime repair exonuclease 1; DNase1L3, deoxyribonuclease 1-like 3; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; TLR9, Toll-like receptor 9; IFN-I, type I interferon; Treg, regulatory T cell; SLE, Systemic Lupus Erythematosus; RA, rheumatoid arthritis; SS, Sjögren's syndrome; MS, multiple sclerosis; ROS, reactive oxygen species; RNS, reactive nitrogen species; mtDNA, mitochondrial DNA; AIT, autoimmune thyroiditis; TPO, thyroid peroxidase; FLS, fibroblast-like synoviocytes; Tg, thyroglobulin; mtDNA, mitochondrial DNA.

and autoantibody production. Salivary gland epithelial cells from patients with SS exhibit increased levels of oxidative DNA damage markers, such as 8-oxoguanine, and show evidence of an activated DDR, including γH2AX (Fig. 4) (85,125,126). This intrinsic genomic stress is considered to contribute to glandular dysfunction and the release of immunostimulatory nucleic acids. The impaired DNA repair capacity observed in patients with SS may accelerate disease progression. Specifically, dysfunction of the BER pathway can lead to ineffective repair of oxidative DNA damage, and unrepaired SSBs may progress into more cytotoxic DSBs (127,128). Furthermore, defective O^6-methylguanine-DNA methyltransferase repair in high-risk patients with SS and a tendency to develop lymphoma further exacerbates genomic instability (129).

Mechanistic model in SS. Defects in DNA clearance or abnormal accumulation of DNA are key drivers of inflammation in SS (130). Concomitantly, cells exhibit inherent defects in DNA repair capacity. This inability to effectively resolve DNA damage leads to the accumulation of lesions and triggers a compensatory hyperactive DNA damage response, manifesting as enhanced p53 phosphorylation and G_1 phase cell cycle arrest (125,131). Mechanistic studies have revealed that unrepaired DNA fragments accumulating in the cytoplasm activate innate immune signaling pathways, particularly the cGAS-STING pathway, leading to excessive production of inflammatory factors. This triggers a type I interferon response, subsequently impairing salivary and lacrimal gland function (Figs. 4 and 5) (132,133). Furthermore, cytokines such as IFN-γ, TNF-α, IL-12 and IFN-α can continuously activate autoreactive T/B cells (128).

Therapeutic significance. Currently, strategies focusing on enhancing DNA repair, reducing oxidative stress or inhibiting downstream signaling are being investigated in preclinical models. For instance, key drugs that inhibit the cGAS-STING pathway, such as rapamycin, have been demonstrated to significantly alleviate pathological damage to the submandibular glands and improve salivary gland function in SS model mice by restricting excessive activation of this pathway (134). Similarly, drugs targeting the TLR pathway, such as inamodine, can mitigate glandular damage and inflammation in experimental SS by inhibiting the activation of NLRP3 inflammasomes (135).

RA

Mechanistic model and clinical evidence of RA. The core pathological features of RA include chronic synovial inflammation, abnormal proliferation and enhanced invasiveness of RA synovial fibroblasts (RA-FLS), and eventual destruction of articular cartilage and bone (Fig. 4) (136). In the RA synovial microenvironment, activated immune cells, including macrophages and T cells, excessively produce and accumulate ROS, which contributes to oxidative stress and perpetuates inflammation (137,138). The persistent inflammation and oxidative stress microenvironment in synovium is a key factor inducing local cellular DNA damage, and the two can form a mutually exacerbating vicious cycle (139). Studies have shown that the abundant pro-inflammatory factors in RA synovium upregulate AIM2 protein by activating NF-κB and other pathways. After recognizing the cytoplasmic dsDNA, the AIM2 inflammasome recruits the adaptor protein ASC through its PYD domain, which then recruits pro-caspase-1 and assembles it into an activation platform, eventually leading to the activation of Caspase-1 (139).

Clinical studies have found that patients with RA not only have increased DNA damage, but also have inherent defects in their DNA repair ability. Compared with healthy controls, the levels of endogenous DNA SSB and DSBs in peripheral blood mononuclear cells of patients with active RA were significantly increased (140). A 2024 study further revealed that the repair efficiency of RA patients' cells for DNA DSBs was significantly lower after induced damage, and this low repair efficiency was related to the single nucleotide polymorphisms of specific genes (such as Rad51) in the HR repair pathway (141). It has been demonstrated that the levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, in the synovial fluid of patients with RA were significantly higher than those in the non-arthritis control group (142). Furthermore, NADPH oxidase 4-mediated oxidative stress in RA-FLS markedly enhances their migration and invasion capabilities, forming a critical pathogenic axis (143). In RA, metabolic and functional abnormalities of immune cells may lead to genomic and mitochondrial instability. For example, elevated levels of mtDNA have been detected in the synovial fluid of patients with RA, suggesting that it may act as a DAMP to drive inflammation (142). This discovery reveals a key pathological mechanism in RA: DNA repair defects and cellular energy metabolism crisis jointly lead to pathological death of immune cells, such as pyroptosis, while released molecules such as mtDNA act as DAMPs to continuously activate the immune system (107). This mechanism closely links DNA repair deficiency, cellular energy metabolism dysregulation and pathological death of immune cells, which provides a key explanation for the persistence of chronic inflammation and immune dysregulation in RA. In addition, cfDNA is a key ligand that activates cGAS-STING and TLR9 pathways in RA and drives inflammation (144). Notably, neutrophil extracellular traps are web-like structures composed of decondensed chromatin and antimicrobial proteins released by activated neutrophils. They contain a large amount of cfDNA (including mtDNA) and citrullinated autoantigen. These substances, as a new wave of cfDNA, aggravate inflammation again through the TLR9/cGAS-STING pathway (Fig. 5) (145). A study has shown that the DNA methylation group of peripheral blood mononuclear cells in patients with RA showed significant changes and increased variability compared with the healthy control group, indicating that the systemic inflammatory state is directly related to epigenetic regulation (146).

Therapeutic implications for RA. These findings provide novel perspectives for precision diagnosis and treatment of RA. Monitoring DNA damage markers such as 8-OHdG and cfDNA not only helps assess disease activity but also predicts treatment response (142,147). Intervention strategies targeting the DDR-inflammation axis, such as modulating epigenetic modifications or using biologics that can indirectly ameliorate DNA repair capacity, may represent novel approaches to break the 'damage-inflammation' vicious cycle (47,148).

SLE

Clinical evidence of SLE. Patients with SLE exhibit marked genomic instability *in vivo*, characterized by oxidative stress-induced DNA damage and accumulation of unrepaired SSBs and DSBs (Fig. 4) (39). The degree of genomic instability is directly related to disease severity. Studies have demonstrated that patients with active SLE exhibit significantly elevated levels of oxidative DNA damage, as indicated by increased plasma 8-OHdG, alongside decreased expression of the repair enzyme OGG1 in leukocytes compared to healthy individuals (149).

Mechanistic model and therapeutic implications for SLE. The pathogenesis of SLE is closely linked to autoantigen

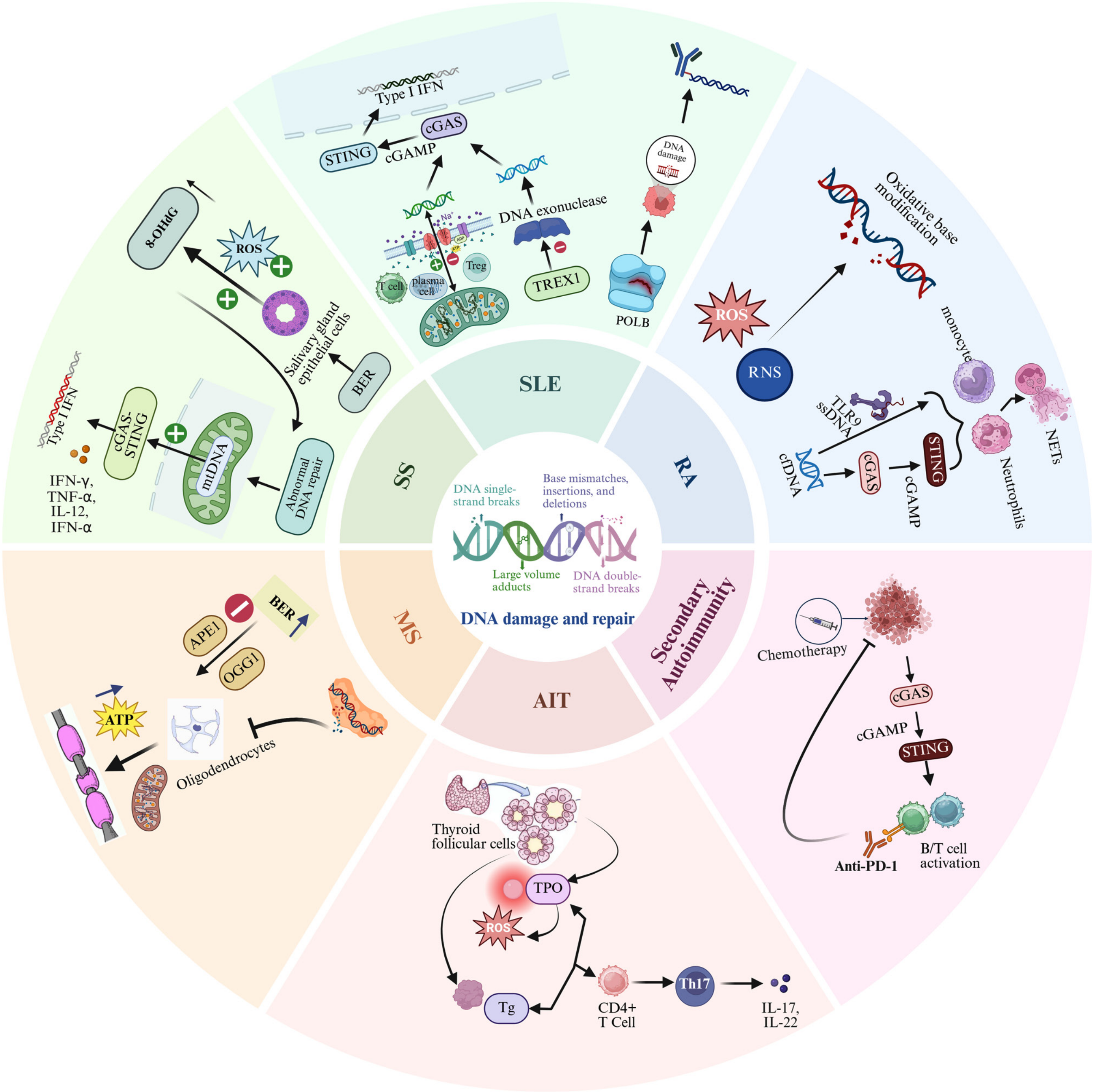

Figure 5. Connection between DNA damage and repair and specific autoimmune diseases. In SS, the BER function fails, leading to the accumulation of salivary gland oxidative damage (such as 8-oxoguanine). Unrepaired DNA fragments accumulate in the cytoplasm, activating innate immune signaling pathways, especially the cGAS standing pathway, resulting in excessive production of inflammatory factors, driving type I interferon storms, and causing glandular atrophy. In RA, synovial fibroblasts undergo base modifications (8-oxoguanine) and BER impairment due to ROS/RNS induction, promoting genomic instability and an invasive phenotype; cfDNA activates NETs via TLR9/cGAS-STING. In SLE, mitochondrial dysfunction-characterized by altered membrane potential and mtDNA release-combined with defective nuclear DNA clearance (via TREX1/POLB) leads to cytoplasmic DNA accumulation. This activates the cGAS-STING pathway in pDCs, driving type I interferon production and autoantibody formation. In MS, downregulation of BER (OGG1/APE1 downregulation) in oligodendrocytes contributes to the accumulation of oxidative damage and myelin regeneration impairment. Autoimmune thyroiditis involves a burst of ROS in thyroid follicular cells inducing DNA breaks, releasing thyroglobulin and activating Th17 inflammation. BER, base excision repair; TREX1, three prime repair exonuclease 1; cGAS, cyclic GMP-AMP synthase; cfDNA, cell-free DNA; SLE, Systemic Lupus Erythematosus; RA, rheumatoid arthritis; SS, Sjögren's Syndrome; MS, multiple sclerosis; ROS, reactive oxygen species; TLR9, Toll-like receptor 9; mtDNA, mitochondrial DNA; dsDNA, double-stranded DNA; RNS, reactive nitrogen species; TPO, Thyroid peroxidase; Tg, Thyroglobulin; OGG1, 8-oxoguanine DNA glycosylase 1; APE1, Apurinic/apyrimidinic endonuclease 1; POLB, DNA polymerase β; pDCs, plasmacytoid dendritic cells; NETs, neutrophil extracellular traps.

exposure resulting from defective DNA repair (150). TREX1 gene mutations represent an important genetic factor in familial lupus (151,152). By impairing the function of the encoded 3'-5' DNA exonuclease, the mutation leads to massive accumulation of undegraded self-DNA in the cytoplasm (42,153). Furthermore, mitochondrial dysfunction serves a pivotal role in the pathogenesis of SLE (154). In patients with active SLE, the mitochondrial membrane potential exhibits marked changes, leading to substantial release of mtDNA into the cytoplasm and activation of type I interferon signaling via the cGAS-STING pathway (155) (Fig. 5). For example, the hypermetabolism of T cells and plasma cells may lead to temporary or persistent elevation of the membrane potential (156,157), while the dysregulation of regulatory B cells may lead to reduction of the membrane potential due to metabolic defects (158). Furthermore, abnormal function of DNA polymerase β promotes autoimmunity through a distinct mechanism (159). One study using mouse models demonstrated that inefficient mutations that reduce polymerase activity impair DNA repair accuracy, producing immunogenic aberrant DNA fragments, which can lead to lupus-like autoimmune diseases (160). Furthermore, impaired clearance of apoptotic cells induced by DNA damage may lead to sustained exposure to nuclear antigens and exacerbate immune complex deposition (161). Macrophages from patients with SLE exhibit markedly reduced phagocytic capacity for apoptotic cells, which is directly associated with disease activity (Fig. 4) (162). Nucleosome fragments released from improperly cleared apoptotic cells can serve as autoantigens to activate autoreactive B cells to produce autoantibodies, establishing a vicious cycle. These findings provide novel targets for the treatment of SLE (161,162). In recent years, small molecule inhibitors targeting the cGAS-STING pathway (such as disulfiram targeting ring finger protein 115, and cordycepin promoting STING degradation) have shown promising efficacy in lupus mouse models, markedly alleviating autoimmune symptoms (163,164). Meanwhile, assessing γH2AX, oxidative damage products, or specific plasma free DNA not only helps assess disease activity but may also provide an important basis for early intervention strategies (165,166).

MS. In MS, a clinical study has confirmed significant oxidative DNA damage and impaired repair function in patients with MS (124). Research indicates increased DNA damage and delayed repair in peripheral blood lymphocytes of patients with MS, alongside downregulated expression of key BER enzymes (such as OGG1 and APE1). These molecular alterations in DNA integrity and repair capacity are implicated in the pathogenesis of MS and correlate with disease activity (Fig. 5) (124). Genetic polymorphisms further associate repair capacity with disease risk (124). This molecular damage has direct clinical relevance: The levels of oxidative DNA markers (such as 8-OHdG) in patient body fluids are positively associated with the severity of core symptoms, including neurological dysfunction, fatigue and cognitive impairment (Fig. 5) (167). Under chronic inflammatory conditions, persistent oxidative stress leads to the accumulation of 8-oxoguanine in DNA. During the attempt to repair this damage, the enzymatic activity of OGG1 itself triggers pro-inflammatory signaling pathways, thereby exacerbating the inflammatory response. OGG1 is a key enzyme for repairing oxidative DNA damage (particularly 8-oxoguanine). An animal study has demonstrated that inhibiting OGG1 activity can ameliorate symptoms of MS (Fig. 5) (85). Notably, epigenetic analyses have revealed abnormal hypermethylation in the promoter regions of specific BER genes within MS lesions, which may represent an important factor contributing to persistent repair dysfunction (168). In addition to nuclear DNA damage, oligodendrocytes in patients with active MS exhibit mitochondrial dysfunction, including markedly reduced membrane potential and ATP production (Fig. 4) (169). Research has demonstrated that the anti-inflammatory effects of small-molecule inhibitors in MS models, coupled with the effective promotion of remyelination by the epigenetic silencing inhibitor ESI1 in animal models of demyelination, together provide a preclinical theoretical foundation for intervening in MS by modulating DNA repair processes (85,168).

Autoimmune thyroiditis (AIT). The pathogenesis of AIT is closely related to oxidative damage in thyroid follicular cells. Thyroid peroxidase (TPO) generates ROS during hormone synthesis, and its dysfunction can exacerbate the oxidative stress state (Fig. 5) (170,171). Excessive ROS can induce oxidative DNA damage, including 8-OHdG. A study has shown that in the thyroid tissue of patients with AIT and in experimental models, the levels of such DNA damage markers are markedly elevated, accompanied by inhibited DNA repair capacity (172). Persistent DNA damage can promote apoptosis of follicular cells, leading to the release of self-antigens such as TPO and thyroglobulin within the cells, thereby disrupting immune tolerance (Fig. 4) (171,172). Additionally, in patients with AIT, autophagosome formation-related genes, such as autophagy-related 101 and beclin 1, have been found to be hypomethylated, and this is associated with environmental iodine levels (173). In thyroiditis animal models, intervening in specific DNA repair mechanisms has been shown to alleviate thyroiditis (172). For example, overexpression of the DNA repair protein mutT homolog 1 (MTH1) can reduce inflammation and damage induced by high iodine levels. High iodine can induce DNA damage and inflammation in thyroid cells by inhibiting MTH1, and increasing the infiltration of Th17 cells in the thyroid (Fig. 5) (172).

Cancer-autoimmune crossover: DDR imbalance in cancer therapy. The DDR in cancer therapy is a double-edged sword, as it is associated with both therapeutic efficacy and the risk of autoimmunity. Chemotherapy-induced DNA damage and tumor cell death can lead to the release of self-antigens and cytoplasmic nucleic acids (such as cytosolic chromatin fragments), which in turn activate innate immune pathways such as the cGAS-STING pathway (174,175). While this drives antitumor immunity, it also provides a theoretical basis for breaking self-tolerance and triggering treatment-related autoimmune phenomena (176,177). In addition, intrinsic defects in DDR genes (such as BRCA1/2 mutations) in tumor cells exacerbate genomic instability and increase tumor immunogenicity (178). While this may enhance the efficacy of immune checkpoint inhibitors, it could also elevate the risk of autoimmune reactions due to aberrant immune activation (178). Therefore, imbalance of the DDR constitutes a key hub linking the therapeutic effects of cancer treatment to autoimmune side effects. A recent study has suggested that precise regulation of the DDR through strategies may enhance antitumor immunity while reducing toxicity to normal lymphocytes, offering a novel direction for optimizing treatment strategies (179).

6. Potential and challenges of DNA damage and repair as therapeutic targets

Building upon the elucidated connections between DNA repair defects and autoimmune pathogenesis, targeting the DDR has

Table II. Summary of therapeutic strategies targeting DNA damage repair pathways.

Therapeutic strategy category	Target/drug	Mechanism of action	Potential therapeutic effect	Research status/ prospects	(Refs.)
PARP inhibitors	Olaparib/Niraparib	Block SSBR via PARP inhibition and reduce autoantigen release	SLE symptom relief; inhibits inflammatory pathways	Effective in Preclinical/ early SLE trials	(182,183,185,189,191)
ATM/ATR kinase inhibitors	AZD0156/VE-821	Activate cGAS-STING pathway by blocking DDR checkpoints	Synergy with immune checkpoint therapy	Effective in preclinical (carcinogenic risk)	(196,198,200,204)
cGAS-STING inhibitors	H-151/C-176	Inhibit STING-TBK1 signaling to reduce IFN-I overproduction	Suppress the activation of autoreactive T cells	Effective in EAE models	(29,45,134)
Antioxidant combination therapy	N-Acetylcysteine	Scavenge ROS, reduces oxidative DNA damage and enhance T cell clearance with immunosuppressants	Reduces disease activity (RA, melanoma)	Significantly reduces recurrence in melanoma models	(205-207)
DNA repair enhancers	OGG1 activators/ XRCC1 analogs	Boost BER to repair oxidative damage and reduce cytoplasmic DNA accumulation	Improve SS gland function, delays immune aging	Validated in XRCC1-deficient mice	(85,124,127)
Nanodelivery Systems	ROS-responsive cGAS inhibitors	Spatiotemporally specific activation/ inhibition of repair pathways and reduces off-target effects	Enhance radio-immunotherapy precision	Entering Phase II trials (radiotherapy + ICI)	(27,31,74)
Epigenetic Modulators	Azacytidine/ HDAC inhibitors	Restore repair gene expression via methylation/ acetylation modulation	Inhibit RA-FLS invasiveness	Synergy in multiple cancer models	(146,148,168)

XRCC1, X-ray repair cross complementing protein 1; ATM/ATR, ataxia telangiectasia mutated/ataxia telangiectasia and Rad3 related; BER, base excision repair; DDR, DNA damage response; DSB, double-strand break; HR, homologous recombination; IFN, interferon; MS, multiple sclerosis; NER, nucleotide excision repair; NHEJ, non-homologous end joining; OGG1, 8-oxoguanine DNA glycosylase 1; PARP, poly adenosine diphosphate ribose polymerase; RA, rheumatoid arthritis; ROS, reactive oxygen species; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSB, single-strand break; TREX1, three prime repair exonuclease 1; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1; EAE, experimental autoimmune encephalomyelitis; FLS, fibroblast-like synoviocytes.

emerged as a promising therapeutic frontier. The integration of mechanistic insights with clinical transformation may reveal novel inhibitor strategies, combination therapies and precision medicine approaches (Table II). However, this path has notable challenges, including balancing efficacy with genomic safety risks and navigating tissue-specific repair dependencies.

Novel therapeutic strategies

PARP inhibitors. PARP inhibitors have achieved significant efficacy in the treatment of breast and ovarian cancer by inhibiting DNA SSBR and inducing a synthetic lethal effect (Table II) (180-182). The repurposing of PARP inhibitors in autoimmune diseases are still at the preclinical exploration stage, and they may exert potential effects by modulating DNA repair and inflammatory pathways (183,184). For example, in EAE model, targeting DNA damage repair related protein PARP-1 can play a therapeutic role by regulating immune cell migration and inflammatory response (183). In addition, a human phase I clinical trial marked the first step in the transformation of a new PARP family inhibitor from preclinical to clinical (184). It is well-established that patients with SLE exhibit defective DNA damage repair. This impairment contributes to the release of self-antigens (such as cfDNA) and the activation of autoimmune responses (39,149).

Challenges and risks associated with PARP inhibitors. Although, theoretically, PARP inhibitors are considered to have therapeutic potential in various autoimmune diseases due to their anti-inflammatory properties and effects on DNA repair, their preclinical exploration in areas such as SLE and MS is still in its early stages (185,186). In addition, long-term use of PARP inhibitors may exacerbate genomic instability. Studies have shown that their prolonged use increases the risk of secondary cancers; for instance, the risk of developing myelodysplastic syndrome/acute myeloid leukemia is significantly higher in patients with ovarian cancer (4-12%) (187). Consequently, rigorous validation of their long-term safety and applicability across heterogeneous patient cohorts remains imperative. Notably, the application of PARP inhibitors in autoimmunity remains controversial with critical safety considerations (188). PARP inhibition alone fails to disrupt the persistent 'damage-inflammation' feedback loop in the inflammatory microenvironment (189). Considering the complexity of the inflammatory microenvironment in RA, theoretically, PARP inhibitors alone may struggle to completely block the progression of the disease (190). Excessive PARP suppression may also impair DNA repair in immune cells. The secondary malignancy risk is a major safety concern (191). Long-term inhibition accumulates unrepaired DNA lesions and increases lymphoma or leukemia incidence, especially in BRCA wild-type individuals (191,192). Another prominent safety issue is hematotoxicity. PARP inhibitors induce myelosuppression, including neutropenia and thrombocytopenia, which may worsen immune deficiency in autoimmune patients (193). To navigate this risk-benefit landscape, future strategies require rigorous validation. Intermittent dosing regimens and nanoparticle-mediated targeted delivery may minimize off-target effects on normal tissues (194,195). Besides, integrating cfDNA damage markers with imaging for long-term safety monitoring is crucial for the early warning and monitoring of autoimmune diseases. Preclinical validation using humanized autoimmune models will further improve translational accuracy (183).

ATM/ATR inhibitors. Inhibitors of ATM/ATR kinase, a central regulator of the DDR, enhance sensitivity to radiotherapy or chemotherapy by blocking cell cycle checkpoints (196,197) (Table II). Emerging studies have found that ATM/ATR inhibitors also promote remodeling of the tumor immune microenvironment through activation of the cGAS-STING pathway (198-200). For example, inhibition of ATR leads to accumulation of unrepaired cytoplasmic DNA, activates cGAS-STING pathway and induces type I interferon secretion, which enhances T cell infiltration and antitumor immunity (200,201). Emerging evidence from preclinical models supports the combination of ATM/ATR inhibitors and immune checkpoint inhibitors (for example, anti-PD-L1) as a promising strategy for synergistic antitumor activity (202,203); however, this strategy necessitates a balance between immune activation and carcinogenic risks arising from unresolved DNA damage accumulation (204).

Combination therapy and precision medicine

N-acetylcysteine (NAC). The antioxidant NAC attenuates oxidative DNA damage by ROS and replenishes the levels of intracellular glutathione, a key antioxidant involved in DNA repair (Table II) (205). Accumulating evidence indicates that NAC monotherapy does not reduce the efficacy of chemotherapy; instead, it protects normal tissues from treatment-induced oxidative injury while preserving the cytotoxic effect of chemotherapeutic agents on tumor cells (206-208). Preclinical and clinical study has indicated that immunotherapeutic agents (such as immune checkpoint inhibitors) reverse the immunosuppressive tumor microenvironment and enhance T cell-dependent elimination of residual tumor cells (209). However, the generalizability of this strategy across different cancer types, the optimal administration timing (for example, concurrent vs. sequential with antitumor agents) and dosage regimens remain to be validated in large-scale clinical trials.

Biomarkers for precision medicine. Damage fragments (such as oxidized base modifications or DSB markers) in cfDNA can be used as biomarkers for real-time monitoring of the DNA repair status (210). For example, persistent high levels of the DNA damage marker γH2AX were detected after radiotherapy suggest insufficient DNA damage repair and may guide the timing of combination therapy with ATM/ATR inhibitor (197,202). In addition, tumor-specific cfDNA mutation profiles (for example, BRCA1/2 deletion) can predict PARP inhibitor efficacy, and immunotherapy responders often exhibit upregulated expression levels of STING pathway-related genes in cfDNA (26,202). Future development of highly sensitive assays and integrated multi-omics modeling is required to improve predictive accuracy.

Key challenges. DNA repair inhibitors face several challenges. PARP or ATM/ATR inhibitors may increase genomic instability in normal tissues due to off-target effects, with long-term PARP inhibitor use potentially inducing hematopoietic malignancies and ATR inhibitors exhibiting hepatotoxicity in mouse models (196,204,211,212). Furthermore, inhibition of specific repair pathways may force cells to rely on error-prone alternative mechanisms (such as microhomology-mediated end-joining), increasing oncogenic mutation risks (213). Significant differences exist in DNA repair capacity and dependency across tissues: Hematopoietic stem cells highly depend on NHEJ, whereas intestinal epithelial cells preferentially use HR (214), leading to notable efficacy and toxicity variations of the same inhibitor in different organs. Strategies addressing these limitations include developing tissue-selective delivery systems and intermittent dosing regimens (194,215). Future research should integrate single-cell sequencing with organoid models to elucidate tissue-specific DNA repair dynamic networks across spatiotemporal dimensions, thereby designing adaptive therapeutic strategies that can adjust according to repair status or cell cycle.

7. Research gaps and priority research agenda

Critical research gaps. Notwithstanding the substantial advances in delineating the DDR-immune axis, critical gaps remain in mechanistic clarity and translational validation. First, the causal temporality between DDR defects and immune activation is still unclear. A study has shown that loss-of-function mutations of TREX1, an endoplasmic reticulum-associated exonuclease, can trigger uncontrolled cGAS-STING activation, which is associated with autoinflammatory diseases, including SLE (216). However, loss-of-function mutations in TREX1 are clearly pathogenic in monogenic diseases such as Aicardi-Goutières Syndrome, but their contribution to complex autoimmune diseases such as SLE still requires more population genetic studies. Second, the role of the cGAS-STING pathway in autoimmunity is contradictory and appears to be dual (152). On one hand, overactivation of this pathway is closely related to type I interferon-driven autoimmunity. On the other hand, animal models suggest that a simple genetic defect (such as TREX1 deficiency) may be insufficient to induce full tissue inflammation, often requiring an environmental 'second hit', indicating that its pathogenicity may be conditional rather than absolutely causative (217). Third, there is currently a lack of clinically validated, standardized DDR-derived biomarkers that can be used for disease stratification or efficacy prediction. Although DDR-related autoantibodies (such as anti-PARP zinc finger domain antibodies) are common in SLE and SS (39,218), biomarkers such as specific damage features of cfDNA, including oxidative modifications, have not yet been prospectively validated as reliable predictive tools, partly due to the lack of standardized detection methods.

Priority research agenda. A prioritized research agenda should address these gaps. Preclinically, using conditional knockout models of specific cells such as synovial cells, the cell-specific role of TREX1-cGAS crosstalk in RA and other diseases was precisely validated (219). In human cohorts, research suggests that specific forms of cfDNA, such as oxidatively modified DNA, may be associated with disease activity (220), providing a basis for its use as a biomarker for monitoring disease activity. A preclinical study suggests that PARP inhibitors may exert therapeutic effects through anti-inflammatory mechanisms, but their inhibitory effects on DNA repair could pose long-term genomic risks (221). Therefore, exploring dosing regimens that can distinguish between their anti-inflammatory effects and genotoxic effects (such as low-dose or intermittent administration) is a key direction for future research.

8. Conclusion

Research on the link between the DDR and autoimmunity has unveiled a complex interplay between genomic instability and immune homeostasis disruption. Unrepaired DNA damage, such as oxidative base lesions or DSBs, can drive autoimmune responses. The core mechanism is that unrepaired DNA damage triggers a type I interferon storm through pathways such as cGAS/STING, while defects in repair genes such as TREX1 lead to exposure of self-nucleic acid antigens, both of which together break immune tolerance and drive self-immunity. Furthermore, epigenetic disorders caused by oxidative stress further exacerbate the functional imbalance of immune cells such as Th17/Treg. Therapeutic strategies targeting DDR pathways show significant potential. Nanomedicines designed to block the cGAS-STING-TBK1 axis can specifically inhibit autoreactive T-cell activation. DNase1L3 analogs help clear free DNA, reducing the autoantigen load and alleviating lupus-like phenotypes in preclinical models. Additionally, combining PARP inhibitors with immune checkpoint blockade represents a promising translational approach by synergistically inducing immunogenic cell death and remodeling the immune microenvironment.

In conclusion, future research should leverage single-cell multi-omics to decipher repair heterogeneity among immune cell subsets and construct dynamic DNA damage maps to reveal the spatiotemporal relationship between lesion accumulation and inflammatory signaling. In addition, the development of novel intervention strategies that can distinguish between anti-inflammatory and genotoxic effects (such as intermittent administration and tissue selective delivery systems) is expected to balance efficacy and safety while avoiding systemic toxicity. These advancements are poised to overcome the limitations of conventional therapies and advance the field of autoimmune disease treatment into the realm of personalized precision medicine.

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Availability of data and materials

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Authors' contributions

KW was primarily responsible for the writing, review and revision of this manuscript. MW, QQX and HF compiled the references and developed the tables and figures. YC, TSZ and XY conceived the structure of the manuscript. LW, JWY and HS drafted the initial manuscript. XF-L and JL participated in the review and the critical revision of the manuscript for important intellectual content. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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