Shimane J. Med. Sci., Vol.43 pp.1-5, 2026

How Genetic Polymorphisms Shape DNA Clearance and Inflammation *In Vivo*

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（Received February 24, 2026; Accepted March 6, 2026; Published online July 6, 2026）

Self-DNA must be efficiently cleared from extracellular spaces, lysosomes, and the cytosol to prevent activation of innate immune sensors such as TLR9 and cGAS–STING. Genetic polymorphisms in nucleases including *dnase1*, *dnase1l3*, *dnase2* and *trex1* impair DNA degradation by reducing catalytic activity, secretion, stability, or expression. These defects allow accumulation of immunostimulatory DNA *in vivo*, promoting type I interferon production, autoantibody formation, and inflammatory diseases. This mini review summarizes key nuclease variants across cellular compartments and their impact on DNA metabolism and immunity.

Keywords: *dnase1*, *dnase1l3*, *dnase2*, *trex1*, cGAS–STING pathway, TLR9

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INTRODUCTION

Self-DNA is usually kept inside the nucleus and mitochondria. However, normal biological processes such as apoptosis, formation of neutrophil extracellular traps（NETs）, erythroid enucleation, and cellular stress constantly produce DNA in extracellular spaces, as well as in lysosomes and the cytosol［1–4］. If this DNA is not quickly removed, it can activate immune sensors, including TLR9 in endosomes and the cGAS–STING pathway in the cytosol. This activation leads to the production of type I interferons and inflammatory cytokines［5–8］. Although these immune responses are important for protecting against viral infections, their long-term activation can cause autoimmune and autoinflammatory diseases.

Several nucleases work together to keep DNA levels under control. DNASE I and DNASE1L3 degrade extracellular DNA, DNASE II breaks down DNA inside phagolysosomes, and TREX1 removes DNA from the cytosol［9–11］. An overview of these compartment specific DNA clearance pathways is shown in Fig. 1. When genetic variants reduce the activity of these enzymes, they lead to persistent self-DNA and inappropriate immune activation, linking nuclease defects to interferonopathies like systemic lupus erythematosus（SLE）, rheumatoid arthritis（RA）, systemic sclerosis（SSc）, and Aicardi–Goutières syndrome（AGS）［12–16］. Although numerous additional variants have been identified

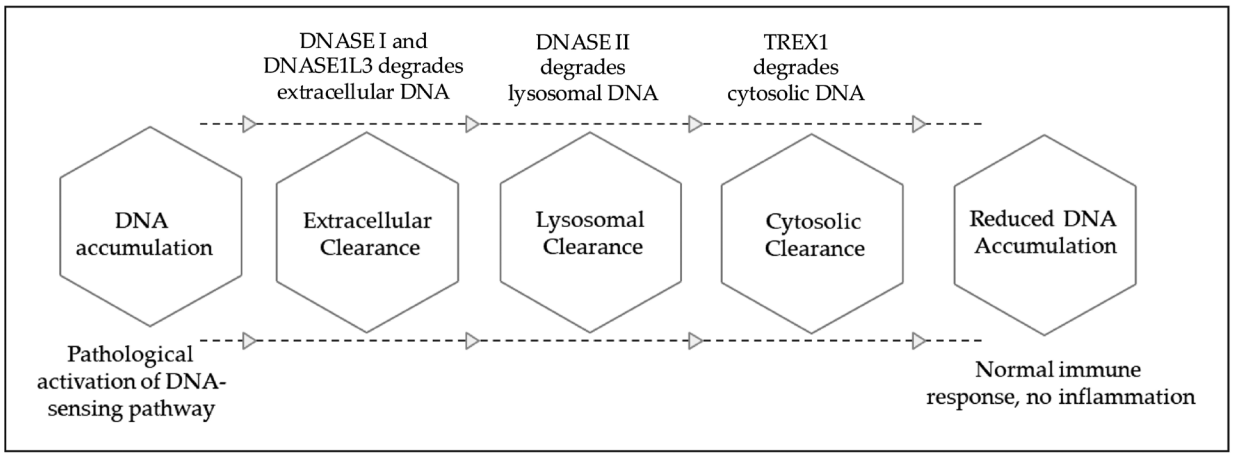

Figure 1. Compartment specific DNA clearance pathways. Schematic overview of extracellular, lysosomal, and cytosolic DNA degradation mediated by DNASE I / DNASE1L3, DNASE II, and TREX1, respectively.

in *dnase1*, *dnase1l3*, *dnase2* and *trex1*, most exhibit minimal functional impact or low population frequency and are unlikely to contribute to disease independently; therefore, this mini-review focuses on variants with demonstrated biochemical and immunological relevance.

EXTRACELLULAR DNA CLEARANCE

Extracellular DNA is continuously released during apoptosis, NET formation, and tissue injury, and must be rapidly degraded to prevent activation of endosomal DNA sensors such as TLR9. Two secreted nucleases, DNASE I and DNASE1L3, form the primary defense against extracellular DNA. DNASE I preferentially digest naked double-stranded DNA, whereas DNASE1L3 is specialized for chromatin-bound and microparticle-associated DNA [17].

Functional polymorphisms in *dnase1*, including p. Gln244Arg and p. Arg107Gly, reduce catalytic efficiency, while promoter variants (−1799 G>A, −637 G>A, −166 C>T) alter transcriptional activity and contribute to lower serum DNASE I levels [18–20]. In *dnase1l3*, the well-characterized p. Arg206Cys variant and the rarer p. G82R impair secretion or reduce catalytic activity [21, 22], resulting in diminished clearance of chromatin rich substrates.

Reduced activity of DNASE I or DNASE1L3 allows NETs and extracellular chromatin to persist, promoting the generation of anti-DNA autoantibodies and formation of immune complexes that deposit in tissues, particularly within renal glomeruli [13]. These processes contribute to the pathogenesis of SLE, rheumatoid arthritis, and systemic sclerosis [12–15], underscoring the essential role of these nucleases in maintaining extracellular DNA homeostasis. The downstream autoimmune consequences of impaired extracellular DNA degradation are summarized in Fig. 2.

LYSOSOMAL DNA CLEARANCE

DNA derived from apoptotic cells, engulfed nuclei, and cellular debris is internalized by phagocytic cells and delivered to lysosomes, where it must be efficiently degraded to prevent aberrant immune activation. DNASE II is the principal nuclease responsible for DNA digestion within acidic phagolysosomes, thereby preventing the accumulation of self-DNA and subsequent activation of inflammatory signaling pathways [23, 24].

Pathological immune activation linked to *dnase2* primarily arises from biallelic loss-of-function variants that abolish enzymatic activity. Disease causing *dnase2* variants include c.347G>C (p. Gly116Ala) and c.362A>T (p. Asp121Val), which affect highly conserved amino acid residues essential for catalytic function [25]. Notably, the c.347G>C variant also disrupts RNA splicing, leading to exon skipping and the production of an unstable or nonfunctional protein [25]. Another pathogenic variant, c.284A>G (p. Tyr95Cys), results in complete loss of DNASE II enzymatic activity [26]. These findings establish DNASE II as indispensable for lysosomal DNA

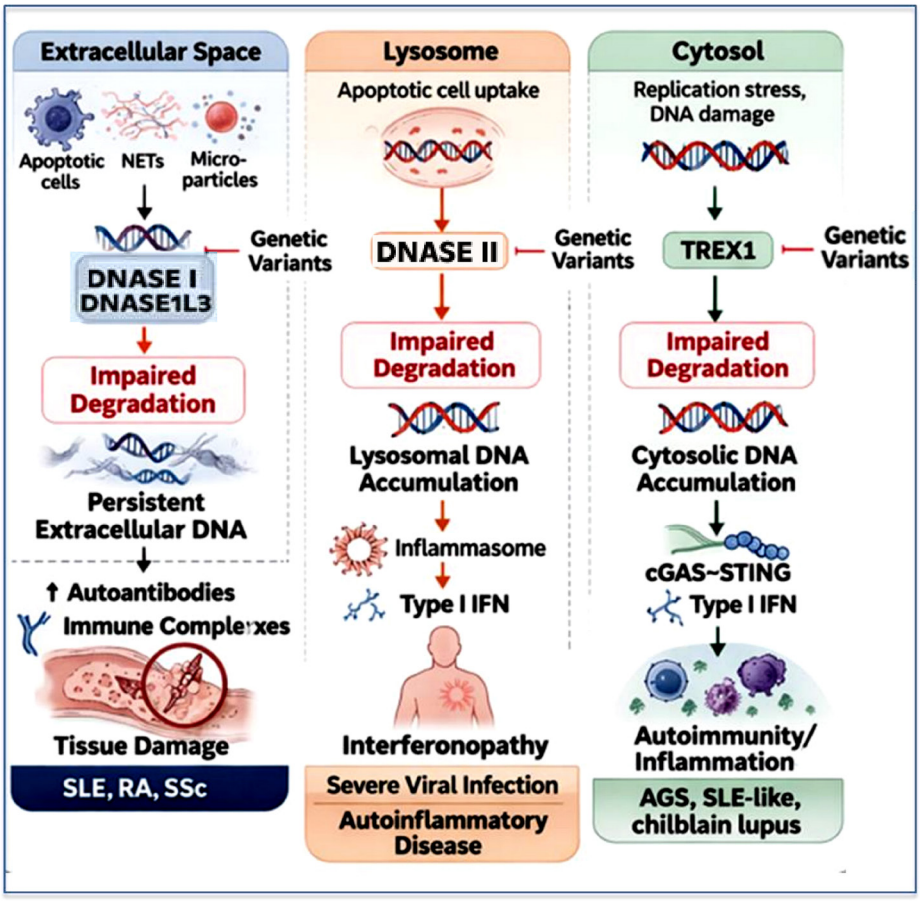

Figure 2. Autoimmune and inflammatory disease resulting from impaired DNA degradation. Genetic variants affecting nucleases involved in DNA clearance led to impaired DNA degradation, accumulation of self-DNA, activation of DNA sensing pathways and chronic inflammation.

clearance, with complete loss of enzymatic activity driving persistent inflammatory signaling and severe interferon-mediated disease. The immunopathological consequences of defective lysosomal DNA degradation are illustrated in Fig. 2.

CYTOSOLIC DNA CLEARANCE

TREX1 is the major cytosolic 3′→5′ exonuclease responsible for degrading aberrant DNA species that accumulate in the cytosol during DNA replication stress, endogenous retroelement activity, or defective DNA repair. Efficient removal of cytosolic DNA by TREX1 is essential to prevent activation of the cGAS–STING pathway and inappropriate type I interferon signaling [27].

Pathogenic *trex1* variants include missense mutations such as p. Asp18Asn and p. Arg114His, which reduce enzymatic activity and are associated with AGS, a severe interferonopathy characterized by neurological abnormalities and elevated IFN-α levels [28, 29]. In contrast, frameshift and truncating variants, including p. Val235fs, abolish TREX1 function and are linked to disorders such as retinal vasculopathy with cerebral leukodystrophy and familial chilblain lupus [30]. Heterozygous missense variants that partially impair TREX1 activity have also been identified in patients with SLE, supporting a model in which incomplete cytosolic DNA degradation predisposes to autoimmunity rather than severe early-onset interferonopathy.

Collectively, these data indicate that loss or reduction of TREX1 exonuclease activity is the critical determinant of cytosolic DNA accumulation and chronic interferon signaling. The convergence of these defects on autoimmune and autoinflammatory disease is summarized in Fig. 2.

CONCLUSION

Genetic polymorphisms that impair DNA clearance reveal how tightly immune regulation depends on proper handling of self-DNA. Across extracellular, lysosomal, and cytosolic compartments, defective nuclease function leads to persistent DNA, chronic type I interferon signaling, and a spectrum of autoimmune and autoinflammatory diseases. Understanding how specific variants alter DNA metabolism provides insight into shared mechanisms of inflammation and may guide development of therapies targeting nucleic acid sensing and clearance pathways.

Ethical Approval

Not applicable.

Author Contributions

S.R. performed the literature review and drafted the manuscript. H.T. supervised and revised the manuscript. K.I., A.A.E., and R.M.T., contributed to manuscript revision. All authors approved the final manuscript.

Acknowledgments

Not applicable

Funding

No funding

Conflict of Interest

The authors declare no conflict of interest.

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