REVIEW ARTICLE

TLR9: an important player in the pathogenesis of systemic lupus erythematosus

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Abstract

Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease marked by the immune system's attack on the body's DNA and related proteins. The exact causes of SLE remain unclear, but recent research highlights the critical role of innate immune receptors, particularly Toll-Like Receptor 9 (TLR9). TLR9 detects unmethylated DNA sequences, including those from pathogens and damaged host cells, triggering immune responses that can either protect against infection or drive autoimmune reactions. In SLE, TLR9 activation varies across immune cell types, leading to diverse effects. For example, TLR9 signaling in B cells may help control autoantibody production, while in dendritic cells, it often promotes harmful inflammation through interferon release. This receptor's dual behavior—acting as both a regulator and an instigator of disease—depends on factors like cell type, genetic background, and environmental triggers. Additionally, interactions with molecules such as vitamin D, estrogen, and High Mobility Group Box 1 protein (HMGB1) further shape TLR9's impact on SLE progression. Understanding TLR9's complex role in SLE could open new avenues for treatment. By targeting specific TLR9 pathways, researchers aim to develop therapies that reduce inflammation without compromising the immune system's ability to fight infections. This review explores TLR9's structure, signaling mechanisms, and its contradictory roles in SLE, offering insights into potential strategies for managing this challenging disease.

Keywords: Systemic lupus erythematosus; Toll-like receptor 9; Innate immunity.

Introduction

It has been demonstrated that either adaptive immunity or innate immunity participates in the pathogenesis of Systemic Lupus Erythematosus (SLE) [1]. Most investigations have been performed to determine the role played by adaptive immunity. Recently, the roles played by innate immunity in the pathogenesis of SLE have been highlighted. Pathogen Recognition Receptors (PRRs) are the main arms of innate immunity that are expressed either on the cell membrane of innate immune cells or secreted by the cells [1].

Among the PRRs, Toll-Like Receptors (TLRs) are more commonly investigated in human immune system-related disorders. Because recognition of self-Double-Stranded DNA (dsDNA) and its associated antigens by the immune system, is one of the main causes of SLE, hence, the main TLRs that recognize dsDNA may be considered the key molecules that participate in the pathogenesis of SLE [2]. Accordingly, TLR9, as the main TLR that recognizes dsDNA/DNA-associated antigens, is considered the main candidate for involvement in the pathogenesis of SLE. It has been reported that TLR9 is expressed in the intracellular vesicles of several immune cells [3]. Due to the complexity of SLE and the involvement of several immune cells in the induction and stimulation of SLE, it has been hypothesized that TLR9 may play different roles in the various immune cells of SLE patients. Thus, investigators may design immunotherapy plans to

limit the severe symptoms of SLE. This review article aims to update the information regarding the roles of TLR9 in the pathogenesis of SLE.

Systemic lupus erythematous; an autoimmune disorder

SLE is a chronic autoimmune disease that is associated with a relapsing and remitting course [1]. It is more prevalent in females than males. Although the exact etiology of SLE is not well understood, it has been documented that environmental and genetic factors, hormones, infection by some viruses like Epstein-Barr Virus (EBV), ultraviolet B exposure, and mental disorders play some roles to triggering immune responses [4]. Accordingly, the activated immune responses lead to the induction of the excessive production of pathogenic autoantibodies against dsDNA and its associated antigens, such as single-stranded DNA binding proteins (SSB), Single-Strand Annealing (SSA), scleroderma 70-kDa antigen, Smith antigen 3, Heterogeneous Nuclear Ribonucleoprotein (hnRNP), etc [5]. The involvement of both adaptive and innate immunity in the pathogenesis of SLE has been demonstrated previously (1). After the production of autoimmune antibodies against dsDNA and its associated antigens, the immune complexes are produced and precipitated in some tissues [1]. The precipitated immune complexes are responsible for activation of the complementary system and some immune system responses, such as antibody-dependent cellular cytotoxicity (ADCC), and subsequently inflammation and damage to the human tissues [6].

The key mechanisms that lead to the induction of the autoantibodies are yet to be clarified. However, it has been hypothesized that innate immunity plays key roles in the recognition of antigens and the induction of adaptive immunity. Therefore, it may be concluded that innate immunity may be considered for the induction of adaptive immunity against dsDNA and its associated antigens. Accordingly, TLR9, as the main PRR for dsDNA and its associated antigens, can be considered a key molecule that participates in the pathogenesis of SLE.

TLR9: structure, ligands, and intracellular signaling pathways

As mentioned in previous sections, TLR9 is the main intracellular receptor for unmethylated CpG-DNA, the DNA of bacteria [3, 7]. 3p21.3 is the location of the TLR9 gene, and the TLR9 related proteins are highly conserved [8]. As with other TLRs, the "N-terminus" of TLR9 contains a Leucine-Rich Repeat (LRR) and is the responsible extracytoplasmic domain for the recognition of unmethylated CpG-DNA [2]. Hydrophobic transmembrane and cytoplasmic Toll/Interleukin 1 Receptor (TIR) domains are the other sections of TLR9 that participate in the induction of intracellular signaling pathways [2]. TLR9 is expressed in lysosomes, endosomes, and the endoplasmic reticulum (ER) [3]. TLR9 recognizes two isoforms of CpG Oligodeoxynucleotides (CpG-ODN), type B/K and type A/D, as primary ligands [3]. Additionally, viral DNA containing unmethylated CpG motifs are another ligand for TLR9 [3]. Interestingly, some evidences suggest that TLR9 could recognize DNA lacking CpG motifs [3]. Therefore, TLR9 can trigger DNA from various sources.

Methods

The main databases, such as ISI Web of Knowledge, Scopus, PubMed, and Google Scholar were searched for TLR9 and systemic lupus erythematous as

keywords. Based on the investigation, 268 papers were found. To refine the search, the review article and the unrelated articles that were not specific for TLR9 and SLE were excluded. Finally, 110 related papers were entered into this review article.

TLR9 roles in systemic lupus erythematous

Recent investigations revealed that TLR9 plays key roles in the pathogenesis of SLE [3]. Accordingly, some investigations revealed that the innate immune receptor may deteriorate clinical symptoms of SLE [9], while others reported the positive roles played by TLR9 against inflammatory responses during SLE [10].

Modulatory effects of TLR9 in systemic lupus erythematous

Although TLR9 is the main receptor for DNA and the activation of immune responses against the macromolecule, some investigations revealed that in some situations, TLR9 is unable to induce pro-inflammatory immune responses following TLR9 ligand interactions and then modulate the functions of immune system cells in SLE patients [11]. For example, it has been reported that inflammatory responses in SLE patients, such as nucleosome-induced neutrophil activation, can happen independently of TLR9 [11]. A study by Tilstra *et al*. (2020) revealed that TLR9 plays different roles in various cells. Accordingly, they reported that TLR9 deficiency in various B cells was associated with deterioration of nephritis, while its deficiency in other immune cells, such as Dendritic Cells (DCs), plasmacytoid DCs, and neutrophils, were not associated with effects on the SLE symptoms in animal models. However, they showed that although the symptoms improved in the animal models of TLR9 deficiency B cells, the titer of anti-nucleosome antibodies was not altered [10]. The study confirmed the results via upregulation of TLR9 in B cells, which resulted in ameliorated nephritis [10]. Gies and colleagues reported that the B cells from SLE patients did not respond with TLR9 ligands to increased production of autoantibodies [12]. The roles played by TLR9 responses at the early transitional B cell stage in B cell tolerance by-pass in limiting the expansion of autoantibody-secreting cells have been documented previously [13]. Lartigue and colleagues reported that TLR9 is required for the production of anti-nucleosome Ab responses, but not anti-dsDNA(14). Bossaller *et al*. (2016) proved the protective roles played by TLR9 and reported that TLR9 deficiency leads to accelerated renal disease in an SLE animal model [15]. Another study confirmed that TLR9 protects B cell autoreactivity in SLE via interaction with other signaling pathways [16]. Although a study by Capolunghi *et al*. (2010) revealed that pharmacological inhibition of TLR9 activation is associated with decreased autoantibody production in either SLE patients in clinical remission or active SLE [17], their investigations were performed on the peripheral blood mononuclear cells but not on the separated B cells. Additionally, a study by Liu *et al*. (2018) revealed that TLR9 is a main inducer of B cell stimulating factor in SLE patients; however, their investigation was not performed on B cells but on the peripheral blood mononuclear cells [18]. The different activities of B cells in comparison to other immune cells in response to TLR9 ligands were also reported by Sieber *et al*. (2014) who revealed that active SLE is associated with a decline in cytokine production by B cells following activation with TLR9 ligands [19]. It appears that TLR9 uses several mechanisms to modulate immune responses during SLE. Moreover, it appears that the

protective roles played by TLR9 in B cells are dependent on the interactions with other intracellular TLRs, such as TLR7 and cytokines [20].

Previous investigations revealed that the transcription factor Aryl Hydrocarbon Receptor (AhR) is a main immunomodulation factor and interactions between apoptotic-cell DNA and TLR9 are the main activators of AhR, which significantly lead to the prevention of immune responses to dsDNA and its associated proteins [21]. Another study proposed that TLR9 regulates B cell functions via upregulation of transcription factors [22]. Thus, it may be concluded that TLR9 plays its roles in a complex microenvironment that may be associated with altered TLR9 functions. In parallel with the hypothesis, the roles of some molecules in the TLR9 microenvironment have been documented previously. Another plausible mechanism for the regulatory effects of TLR9 on B cells in SLE patients may be related to the modulator roles of excess IgG concentrations, via negative feedback on B cells [23]. Therefore, it seems that TLR9 is a regulatory molecule against SLE, when the molecule interacts with its ligands in the B cell system in some stages of B cell maturation and in association with regulatory molecules, such as vitamin D3, and excess IgG concentration that negatively regulates B cell functions.

TLR9 increased inflammation and production of autoantibodies in the systemic lupus erythematous patients

In contrast with the mentioned investigations, several reports demonstrated that TLR9 is a main part of induced inflammation in SLE patients [24]. However, the majority of studies evaluated TLR9 in a complex cell system, but not in B cell systems. Accordingly, some investigations revealed that increased expression of TLR9 is associated with poor prognosis in SLE patients and that corticosteroid treatment is unable to affect TLR9 expression in some SLE patients [24].

Previous investigations revealed that mitophagy, a natural process for the removal of damaged mitochondria via autophagy, is defective in patients with SLE [9]. Accordingly, Xu and colleagues reported that mitophagy is dysregulated in SLE patients and is associated with increased inflammation in TLR9-dependent manner [9]. In another word, dysregulated mitophagy is the main mechanism for presenting self-dsDNA in pathological format to TLR9, which may induce SLE.

Another investigation by Rizzello *et al*., demonstrated that intracellular osteopontin, a multifunctional non-collagenous matrix phosphoprotein, protects inflammatory responses in SLE patients by inhibiting the TLR9-myeloid differentiation primary response (MyD88) signaling pathway [9]. The significant roles played by TLR9 in the chronic production of type I interferon (IFN-I) by Plasmacytoid Dendritic Cells (pDCs) have also been documented by Chaudhary and colleagues [9] and Mortezagholi and colleagues [25]. The results were also confirmed by another study, which revealed that TLR9 is an important molecule to induce the production of anti-dsDNA antibodies [26]. SB431542 is a chemical component and potent inhibitor of the transforming growth factor-beta (TGFβ)/Activin/NODAL pathway and Xia *et al*. (2022) revealed that SB431542 can improve SLE symptoms via inhibition of the TLR9 signaling pathway [27]. Another study showed that expression levels of TLR9 have positive correlations with SLE disease activity in a Chinese population [28]. It appears that the roles of TLR9 in SLE pathogenesis are too complex and are associated with the involvement of several molecules. Accordingly,

Rao et al. reported that TLR9 significantly increased the production of IL-6, an inflammatory cytokine, and ds-DNA, and altered the expression of Inducible Co-Stimulator (ICOS) and Foxp3, the important molecules to regulate immune responses. Previous investigations revealed that Pyruvate Kinase M2 (PKM2), which governs the last step of glycolysis, is upregulated in macrophages, DC and B cells of SLE patients and PKM2 promotes TLR9 pathways and consequently increases the expression of pro-inflammatory molecules [29].

In agreement with the results, several investigations reported that upregulation of TLR9 and the positive roles played by this receptor in the induction of autoantibodies and inflammation in SLE patients [17]. TLR9 can trigger granulopoiesis and type I IFN production by neutrophils [9]. TLR9 induces the pathological roles via several intracellular molecules, including B-cell Activating Factor (BAFF) [30]. It has been demonstrated that Invariant Natural Killer T (iNKT) recognizes lipid antigens on the B cells in CD1d-dependent to maintain autoimmune tolerance, a process that is disrupted in SLE [31]. Accordingly, a study by Liu *et al.* (2015) revealed that TLR9 decreases expression of CD1d on B cells in SLE patients indirectly via upregulation of miR-155 [32]. TLR9 also downregulates blood dendritic cell antigen 2 (BDCA2) expression on human Plasmacytoid Dendritic Cells (pDCs) in the SLE patients, the main molecule to regulate pDCs functions [33]. TLR9 also promotes activation of immune cells during the active phase of SLE by inducing transmembrane Endoplasmic Reticulum (ER) protein, uncoordinated 93 homolog B (UNC93B), expression, the molecule participates in trafficking TLR9 to the endolysosome from the ER [34]. Thus, it seems that there is positive feedback between TLR9 and UNC93B in the SLE patients. TLR9 also induces humoral immunity and nephritis via upregulation of B cell maturation antigen (BCMA) and nephritogenic gp70 autoantigen [35]. Lamphier *et al*. (2006) have a hypothesis that TLR9 may be associated with a breakdown in the normal ability to distinguish self and foreign DNA in SLE patients [36], and it may be because of dysregulated mitophagy. It appears that Fc gamma receptor IIa (FcRIIa)), which is known as Cluster of Differentiation 32 (CD32), plays key roles in activation of immune responses via delivering SLE-immune complexes to intracellular lysosomes containing TLR9 [37]. Therefore, it may be hypothesized that either wrong recognition of self-dsDNA by TLR9 or defective exposure of self-dsDNA to TLR9 are likely responsible mechanisms for defective tolerance to self-dsDNA. In addition to self-dsDNA, the roles played by TLR9 in the recognition of foreign DNA to induce anti-dsDNA and the induction of SLE have also been well demonstrated [38]. Accordingly, it appears that TLR9 and its MyD88-dependent signaling pathway are significantly required for isotype switching to pathogenic autoantibodies in SLE [38]. TLR9 also upregulates C3, a complementary system molecule, in TGFβ1 dependent manner [39,40].

Due to the results, it seems that TLR9 is a main molecule that induces immune responses against dsDNA and its associated proteins, and the pathological roles are induced via wrong recognition and exposure to self-dsDNA in wrong way. In the kidney of SLE animal models, Notch-1 is the responsible transcription factor for upregulation of TLR9 and induction of glomerulonephritis [41]. Therefore, the inflammation may also be another side effect of ectopic expression of TLR9 in SLE patients. To confirm the pathological roles of

TLR9 in SLE, traditional medicine can improve clinical manifestations in a TLR9-dependent manner. For example, a study on the Chinese population revealed that herbal therapy with Jieduquyuziyin Prescription (JP), a traditional Chinese medicine formula, was associated with decreased expression of TLR9 and MyD88, and subsequently decreased inflammation and improved clinical manifestations [42]. Thus, regulation of TLR9 pathways can be considered for future molecular therapy.

TLR9 polymorphisms and systemic lupus erythematous

In addition to microenvironmental factors, genetic polymorphisms within the TLR9 gene may be considered a risk factor for SLE. However, meta-analyses did not show the role of TLR9 genetic polymorphisms in SLE. Due to the fact that meta-analyses reported more valid data than cross-sectional studies regarding the polymorphisms within human genes, this review article only reported the meta-analyses. Accordingly, studies on the Indian Tamil population with a high incidence of SLE revealed that TLR9 rs187084 and -1237C/T polymorphisms are significantly associated with increased expression of TLR9 [44].

Meta-analysis of reported data regarding the TLR9 (-1237C/T) polymorphism demonstrated that the polymorphism does not correlate with SLE susceptibility in either Caucasians or Asians [45]. Meta-analysis studies also revealed that none of the rs187084, rs352140, rs5743836, or rs352139 polymorphisms within the TLR9 gene were associated with SLE risk in Asian and Mexican patients [46]. A research article that was not evaluated in the meta-analysis papers also confirmed the results and reported that rs352140, rs5743836, and rs352139 polymorphisms of TLR9 were not associated with SLE, but they revealed that rs187084 polymorphism had a significant correlation with SLE [47]. Collectively, the analysis declined to identify the roles of genetic polymorphisms within the TLR9 gene in the pathogenesis of SLE.

Which factor determines the outcome functions of TLR9 in systemic lupus erythematous

Although some of the mentioned microenvironmental factors affect TLR9 functions, it appears that TLR9 plays its role during SLE in dependence on several factors. For example, a study demonstrated that 17β-Estradiol enhanced TLR9-related inflammatory responses in mouse spleen B cells [48]. IgE, but not self-IgE, also modulates pro-inflammatory responses by TLR9 in the SLE patients [49]. Additionally, it has been reported that the results from various strains of SLE animal models are different, and TLR9 plays different roles in each strain [50]. It seems that the source of TLR9-ligands is also important to trigger the TLR9 responses. For example, extracellular but not intracellular high mobility group box 1 protein (HMGB1) can induce TLR9 involvement in inflammation via promoting DNA accumulation in endosomes [51]. As mentioned in the previous sections, TLR9 can induce expression of IFN-α to regulate immune responses against dsDNA and its associated antigens (9). Previous investigations revealed that excess C-Reactive Protein (CRP) can suppress the effects of TLR9 and the production of IFN-α, as a regulator of immune responses [52]. Other molecules, such as progranulin (PGRN) and IL-21, which are the soluble cofactors for activation of TLR9 signaling by CpG-DNA, can also direct the roles of TLR9 in SLE patients [53]. While Carabin, a negative regulator of B lymphocytes, deficiency in B cells increases TLR9-related autoimmunity in SLE

patients [54], thus, increased expression of some TLR9-related molecules may affect the potential roles of TLR9 in the pathogenesis of SLE. Additionally, due to some investigations, it appears that the expression of TLR9 in various tissues is different in SLE patients when compared to healthy controls. For example, although several investigations reported upregulation of TLR9 in the PBMCs, the expression of the molecule is lower in the cervical epithelial cells of SLE patients in comparison to healthy controls [55].

The ligand types also affect TLR9 functions, for example, inhibitory CpG oligonucleotide attenuates inflammatory reactions during SLE [9]. Moreover, it appears that the type of B cells may be another intervention factor in TLR9 function. For example, Papadimitraki *et al.* (2006) revealed that increased expression of TLR9 in memory B cells but not naive B cells plays key roles in the induction of anti-dsDNA in SLE patients [56].

The roles played by other intracellular molecules in the regulation of TLR9 during SLE have also been reported. For instance, it has been demonstrated that the Bruton Tyrosine Kinase (Btk) is a necessary factor for anti-DNA antibody production during SLE [57]. Accordingly, Halcomb and colleagues reported that Btk directs TLR9 responses to be an inflammatory reaction and decreased expression and functions of Btk can be associated with modulatory effects of TLR9 [57]. It seems that the model of the study is a main factor in determining TLR9 activities. For example, a controversial study demonstrated that TLR9 plays an activator role in B cells for the production of anti-dsDNA antibodies in an animal model of SLE [57]. In addition, the cell system can also affect the role of TLR9. Accordingly, some data also demonstrated that pDCs show similar functions to B cells in response to TLR9 ligands [58]. TLR9-dependent effects of pDCs are dependent on the cell systems, such as neutrophil extracellular traps [59]. As TLR9 exhibits cell-specific and context-dependent roles in SLE (Figure 1), targeted modulation of its signaling pathways has emerged as a promising therapeutic strategy (Table 1).

Current approaches range from oligonucleotide inhibitors to herbal formulations, each addressing distinct aspects of TLR9 dysregulation. Table 1 summarizes therapeutic agents that modulate TLR9 signaling pathways, their mechanisms of action, experimental evidence from in vitro and in vivo studies, current development stage, and corresponding references from the literature.

Table 1: Experimental and clinical TLR9-targeted therapies for systemic lupus erythematosus

Therapeutic Agent	Mechanism of Action	Experimental Evidence	Current Stage	Reference
Inhibitory CpG oligonucleotides	Blocks TLR9 activation by competing with DNA ligands	Reduces autoantibody production in PBMCs from SLE patients; attenuates nephritis in murine models	Preclinical	[36]

Continued...

Jieduquyuziyin prescription (JP)	Downregulates TLR9/MyD88 signaling pathway	Decreases TLR9 expression, reduces inflammation, and improves atherosclerosis in SLE patients	Clinical trial (Traditional Chinese Medicine)	[18]
SB431542	Inhibits TLR9-TGFβ1-PDGFB axis	Improves SLE symptoms by reducing IL-6, dsDNA, and renal pathology in mice	Preclinical	[41]
Vitamin D3	Suppresses TLR9 expression in PBMCs	Reduces pro-inflammatory cytokine production in SLE patients	Adjunctive therapy	[53]
Shaoyao-Gancao Decoction	Modulates TLR9-mediated NETosis	Attenuates neutrophil extracellular trap formation in MRL/lpr mice	Preclinical (Herbal)	[43]
IVIg (Intravenous Immunoglobulin)	Attenuates TLR9 activation in B cells	Reduces anti-dsDNA antibody production in SLE patients	Clinical use (off-label)	[56]

PBMCs: peripheral blood mononuclear cells; NETosis: neutrophil extracellular trap formation; MRL/lpr mice: murine lupus model; IVIg: intravenous immunoglobulin; SLE: systemic lupus erythematosus

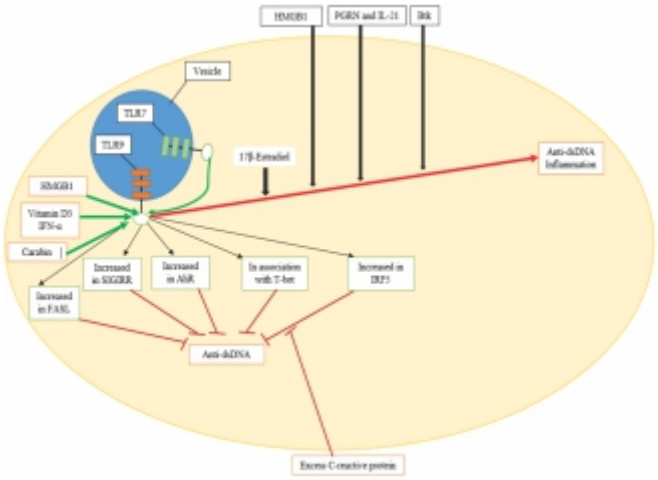

Figure 1: The plausible mechanisms used by TLR9 in the regulation of anti-dsDNA responses and the factors that affect its functions in SLE patients. TLR9 activities can be affected by several intracellular signaling pathways, such as TLR7, and regulatory factors, such as interferon-alpha (IFN-α), vitamin D3, carabin, and intracellular HMGB1. TLR9 suppresses the induction of anti-dsDNA responses via upregulation of FAS Ligand (FASL), Single Immunoglobulin Interleukin-1 Receptor-Related molecule (SIGIRR), Aryl Hydrocarbon Receptor (AhR), and Interferon Regulatory Factor 5 (IRF5). TLR9, in association with T-bet, suppresses anti-dsDNA production. Extracellular HMGB1, 17β-Estradiol, Progranulin (PGRN), IL-21, and Bruton Tyrosine Kinase (Btk) are the main inducers of the pro-inflammatory roles of TLR9 in SLE patients.

Discussion

The involvement of TLR9 in SLE presents a fascinating yet challenging paradox. As a sensor of DNA, TLR9 is uniquely positioned to influence autoimmune responses, but its effects vary widely depending on cellular and molecular contexts. In some cases, TLR9 activation suppresses harmful immune reactions, while in others, it fuels the inflammatory processes that characterize SLE.

One key factor in TLR9's dual role is its expression in different immune cells. In B cells, TLR9 signaling can limit the production of autoantibodies by promoting inhibitory pathways involving molecules like FASL and AhR. This regulatory function suggests that enhancing TLR9 activity in B cells might benefit certain SLE patients. However, in Plasmacytoid Dendritic Cells (pDCs), TLR9 stimulation often leads to excessive interferon production, a major driver of SLE symptoms. This opposing effect underscores the need for precise, cell-specific targeting in potential therapies.

The microenvironment further complicates TLR9's behavior. Hormones like estrogen amplify TLR9-mediated inflammation, which may explain why SLE is more common in women. Conversely, vitamin D can dampen TLR9 signaling, offering a possible explanation for the observed benefits of vitamin D supplementation in some patients. Other molecules, including HMGB1 and progranulin, also modulate TLR9 activity, either worsening or alleviating disease manifestations.

Genetic studies have yet to find strong links between TLR9 polymorphisms and SLE susceptibility, but variations in TLR9 expression or function could still influence disease severity. Additionally, interactions between TLR9 and other receptors, such as TLR7, create complex signaling networks that shape autoimmune responses. Disrupting these networks with targeted inhibitors might provide new treatment options, but achieving the right balance is critical to avoid unintended immunosuppression. Emerging therapeutic approaches include synthetic TLR9 inhibitors and traditional medicines like Jieduquyuziyin, which have shown promise in reducing inflammation in preclinical studies. However, translating these findings into effective human treatments requires a deeper understanding of TLR9's context-dependent roles. Future research should focus on identifying biomarkers to predict individual responses to TLR9 modulation, enabling personalized therapies.

In summary, TLR9's contradictory roles in SLE reflect the intricate balance between immune defense and self-tolerance. Its capacity to both aggravate and mitigate disease highlights the importance of context in designing interventions. By unraveling the precise mechanisms governing TLR9's actions, researchers can develop smarter strategies to reprogram immune responses in SLE, offering hope for more effective and tailored treatments. This review emphasizes the need for continued exploration of TLR9 biology to unlock its full therapeutic potential in autoimmune disease management.

Conclusion

The role of TLR9 in SLE presents a complex paradox that can both bolster immune defense and promote autoimmunity. Its impact is context-dependent, varying by tissue and target cells and promoting autoantibody restraint in B cells but driving interferon production in plasmacytoid dendritic cells. Environmental factors like hormones and vitamin D modulate TLR9 pathways, amplifying or dampening its effects. Identifying

biomarkers and developing cell- and tissue-specific therapies are essential for improving SLE clinical management.

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