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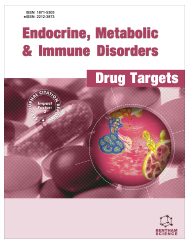
REVIEW ARTICLE

The Role of the Toll-Like Receptor Signaling Pathway in Autoimmune Diseases and Treatment with Traditional Chinese Medicine: A Literature Review



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Abstract: Toll-Like Receptors (TLRs) is a pattern recognition receptor that connects innate and adaptive immunity and participates in inflammatory responses play a key role in common autoimmune diseases such as Rheumatoid Arthritis (RA), systemic lupus erythematosus (SLE), psoriasis, and Sjögren's syndrome (SS) by participating in antigen recognition, immune cell activation, and inflammatory factor release. Due to the multi-component and multi-target characteristics of traditional Chinese medicine (TCM), the role of TCM active ingredients acting on TLRs has been widely studied. This article describes the relationship between TLR and four autoimmune diseases, as well as a review of the efficacy of TLR intervention by active ingredients of traditional Chinese medicine. To provide some basis for the future clarification of the mechanism of action of drugs for autoimmune diseases and to assist in the development of new medicines.

Keywords: Toll-like receptor, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, traditional Chinese medicine.

1. INTRODUCTION

Autoimmune diseases are a group of diseases characterized by the misdirection of the immune system to its host, affecting about one in ten individuals, with prevalence and incidence evolving with gender, age, socio-economic status, and season [1]. The pathogenesis of autoimmune diseases is the result of a complex combination of genetic, epigenetic, environmental factors, and immune regulation. Environmental factors trigger susceptibility genes, leading to immune co-functioning dysfunction, abnormal activation and proliferation of immune cells, autoantibody production, and the release of large quantities of inflammatory factors, which in turn produce multi-system damage [2, 3]. Toll-like receptors (TLRs) are pathogen-specific recognition receptors of the innate immune system, which can also be involved in the induction of adaptive immune responses, expressed on different immune cells, and involved in the pathogenesis of a variety of autoimmune disorders through activation of downstream signals, induction of cytokine production and immune cell proliferation. Such as rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and psoriasis [4-6]. In recent years, the role of Traditional Chinese Medicine (TCM) in the treatment of autoimmune diseases by acting on TLRs and thus activating downstream signaling pathways has been gradually explored. Therefore, this article summarizes the relationship between the Toll-like receptor pathway and several autoimmune diseases and the latest progress of TCM in the treatment of autoimmune diseases through TLR.

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2. TLR

2.1. TLR Families and Ligands

TLRs are the most well-described class of Pattern-Recognition Receptors (PRRs), originally discovered in Drosophila embryos [7]. It can distinguish between self and foreign pathogens by recognizing Pathogen-Associated Molecular Patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [8, 9]. The TLR family in humans consists of 10 members (TLR1-TLR10), which have specific ligands, expression profiles, and cellular localization [10]. Among them, TLR1, TLR2, TLR4, TLR5, TLR6, and TLR10 are localized on the cell surface and mainly recognize lipids, lipoproteins, proteins, and other membrane components of microorganisms. Meanwhile, TLR3, TLR7, TLR8, and TLR9 are expressed in intracellular vesicles and recognize nucleic acids from pathogens or their nucleic acids in the disease state [11]. TLRs recognize natural exogenous ligands as well as natural endogenous ligands and secreted ligands

[12]. Different TLRs have different functions in ligand recognition and immune responses, and different TLRs can be combined to form heterodimers, thus extending the range of pathogens recognized. TLR2 has a wide range of ligands, recognizing bacterial lipopeptides, lipoproteins, lipotropic acids (LTAs), Lipoarabinomannan (LAMs), and yeast polysaccharides, among others [13]. TLR2-TLR1 can recognize tri-acylated lipopeptides from Gram-negative bacteria. A diacyl phosphatidylethanolamine from the cell membrane of Akkermansia muciniphila is also recognized by TLR2-TLR1 heterodimers [14]. TLR2-TLR6 can recognize diacylated lipopeptides from Mycoplasma species [15, 16]. TLR4 recognizes Gram-negative bacterial lipopolysaccharide (LPS), heat shock proteins (HSPs) released by host necrotic cells [17], and the high mobility group box-1 (HMGB1) [18]. TLR5 recognizes flagellin proteins, e.g., Pseudomonas aeruginosa, Bacillus subtilis, and Salmonella typhimurium that have flagellin proteins can be recognized by TLR5 [19-21]. TLR3 specifically recognizes Double-stranded RNA (dsRNA), an intermediate product of viral replication, and polyinosinic-polycytidylic acid (Poly(I: C)) [22]. TLR7 and TLR8 are closely related, share the same intracellular body location and ligands, and both recognize single-stranded RNA (ssRNA) from viruses, as well as low-molecular-weight imiquimods of the imiquimod family, R-848, etc [23, 24]. TLR9 recognizes single-stranded DNA containing unmethylated cytidine-phosphoguanosine (CpG) motifs in bacteria or viruses [25]. TLR10, on the other hand, is thought to be an orphan receptor whose ligand and function are unknown. Still, studies have shown that the ligand binding pocket of TLR10 is similar to that of TLR2, suggesting that they can recognize the same or overlapping ligands [26], In addition, the TLR2/TLR10 heterodimer can play a role in lipopolysaccharide recognition in helicobacter pylori [27], it has been shown that TLR10 can detect the HIV-1 gp41 protein [28].

2.2. TLR Signaling Pathway

TLRs are type I transmembrane proteins composed of extracellular structural domains with leucine-rich repeat sequences for ligand recognition, as well as transmembrane structural domains and cytoplasmic regions. The cytoplasmic portion of the TLRs bears a high degree of similarity to the IL-1 receptor family and is referred to as the Toll/IL-1 receptor (TIR) structural domain [29]. Activation of the TLR signaling pathway originates from the cytoplasmic TIR structural domain. Upon recognition of a ligand by a TLR extracellular structure, a signal is generated that causes the TIR structural domain to interact to recruit adapter molecules. The mechanism of the signaling pathway varies depending on which ligand the TLRs bind. The major adapters are myeloid differentiation primary response protein 88 (MyD88), MyD88-adaptor-like (Mal, also known as TIR domain-containing adaptor protein or TIRAP), TIR-domain containing adaptor protein inducing interferon-β (TRIF), TRIF-related adaptor molecule (TRAM), SARM (sterile-α and armadillo motif-containing protein), and SARM can negatively regulate TRIF-dependent pathways [30, 31]. TLR signaling can be classified into two pathways according to the TIR adapters they contain: the MyD88 pathway (MyD88-dependent pathway) and the TRIF pathway (MyD88-independent pathway) [32]. TLR4 is the only TLR that activates both pathways [33] (Fig. (**1**).

MyD88 is a universal adaptor protein for all TLRs except TLR3, and TLR4 and TLR2 (including dimers with TLR1 or TLR6) require TIRAP to recruit MyD88 [34, 35]. In contrast, TLR5 and TLR7-9 can interact with MyD88 alone. Upon receiving stimulation from the ligand, the n-terminal death structural domain of MyD88 recruits IL-1 receptor-associated kinase 4 (IRAK-4) and IRAK-1, which, when phosphorylated by activated IRAK-4, binds to tumor necrosis factor receptor (TNFR)-related factor 6 (TRAF-6). Subsequently, TRAF6 can recruit the ubiquitin E2-binding enzyme complex (UBC13 and UEV1A), which in turn recruits and activates the TAK1 complex (the TAK1 protein kinase complex consists of it with the regulatory subunits TAB1, TAB2, and TAB3) and the IKK complex (consists of IKKα, IKKβ, and NEMO (a regulator of NF-κB signaling)) resulting in a decrease in NF- κB and MAPK signaling pathways activation and induction of inflammatory cytokines [36, 37]. In one pathway, the IKK complex phosphorylates the inhibitory protein of NF- κB, IκB, leading to its proteasomal degradation, which allows the translocation of NF-κB to the nucleus and triggers the transcription of a range of proinflammatory factors. Another pathway is that activated TAK1 simultaneously activates MAPK family members JNKs and p38 by inducing the phosphorylation of MAPK kinases 4/7 (MKK4/7) and MKK3/6 [38]. In addition, TLR7-9 on the surface of plasmacytoid dendritic cells (pDCs) can activate IRF7 in a cell-specific manner through the MyD88 pathway upon ligand stimulation, which in turn leads to the production of Type I Interferons [39].

The TRIF pathway is responsible for type I interferon (IFN-I) production, and upon ligand stimulation, TLR3 can connect directly to TRIF proteins [40]. TLR4, on the other hand, requires TRAM to bridge to TRIF [41, 42]. Within the TRIF pathway, including but not limited to TRAF3, TRAF3, IKKi/IKKe, and TBK1, ultimately leads to the activation of IRF3 and IRF7, which results in the transcription of IFN-I in the nucleus [43]. In addition, TRIF stimulates RIP1 and TRAF6, leading to the activation of MAPKs and NF-kB [32, 44].

3. TLR AND AUTOIMMUNE DISEASES

3.1. TLR and Rheumatoid Arthritis

RA is a chronic inflammatory joint disease primarily characterized by polyarticular synovial inflammation with symmetrical involvement of small and large joints [45]. Between 1980 and 2019, the global prevalence of RA was 460 per 100,000 people [46]. Although the etiology of RA is unknown, the factors that influence it have been extensively studied. The most significant risk factor for RA is genetic, with a first-degree relative with rheumatoid arthritis increasing the risk of developing the disease by two to five-fold

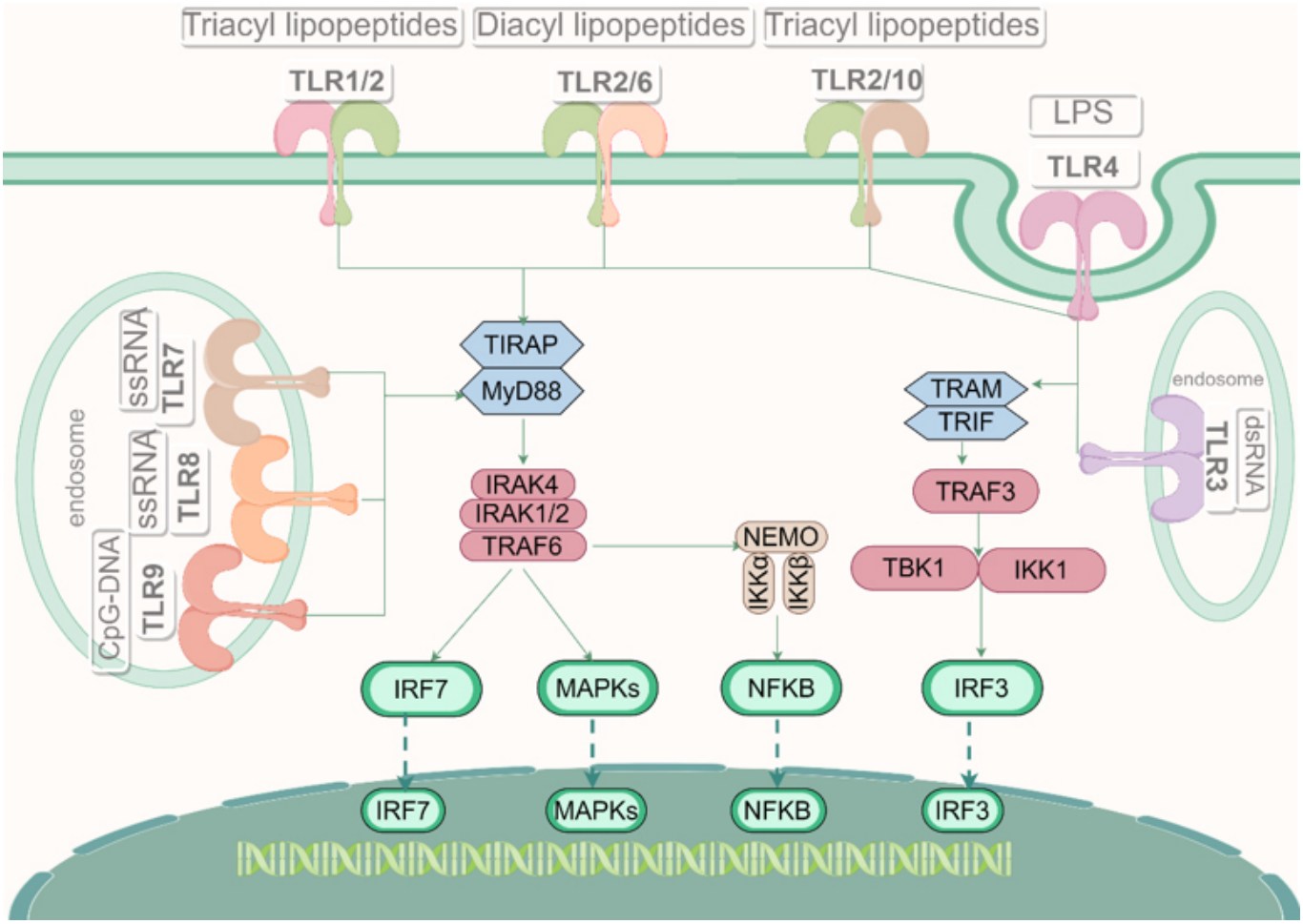

Fig. (1). The TLR family structure consists of three parts: the extracellular structural domain, the transmembrane structural domain, and the TIR structural domain. When the TLR extracellular structure recognizes a ligand, it generates a signal that causes the TIR structural domain to interact with each other to recruit different adapter molecules, thereby activating the NF-kB, MAPKs, and IFN signaling pathways. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

[47]. In addition, many environmental factors, such as smoking, alcohol consumption, diet, obesity, and environmental pollution, are also associated with the development of RA [48]. Early diagnosis is clinically crucial in the treatment of RA, as in up to 90% of patients, early diagnosis and treatment can stop or slow down the progression of the disease, thus preventing irreversible disability [49]. RA affects not only the joints but also other tissues and organs such as the heart, lungs, and kidneys [50-52], etc. Significant results have been achieved in the understanding of the pathogenesis of RA: firstly, the early production of autoantibodies in response to genetic and environmental stimuli, leading to systemic immune dysregulation of the mucosal surfaces, and secondly, the appearance of clinical symptoms, synovial hyperplasia, and infiltration of immune cells leading to joint damage [53]. When synovial dendritic cells are activated, they increase the release of factors such as IL-1, IL-6, IL-12, IL-23, and tumor necrosis factor-alpha (TNF-a). These cytokines are known to induce the differentiation of $CD4^+$ T cells into inflammatory T helper 1 (Th1) [54], Th17 [55], and Follicular helper T (Tfh) cells [56]. Among them, Th17 cells in turn secrete IL-17, IL-21, IL-22, and granulocyte-macrophage colony-stimulating factor (GM-CSF), which are involved in chronic inflammation of the synovium. Meanwhile, IL-17A of the IL-17 family can promote bone erosion, cartilage destruction, and neoangiogenesis in RA patients [57]. Tfh cells are known to be able to promote bone erosion and neoangiogenesis in RA patients through their surface molecules C-X-C chemokine receptor type 5 (CXCR5), inducible costimulatory molecule (ICOS), and programmed cell death 1 (PD-1), and secreted cytokines are involved in the regulation of RA [58]. As a bridge between innate immunity and adaptive immune response, TLR can play a key role in rheumatoid arthritis by presenting antigens, inducing the release of inflammatory factors, and T-cell differentiation Fig. (**2**). It has been shown that multiple TLR agonists induce IL-23 production by DCs, e.g., LTA (TLR2), LPS (TLR4), and R848 (TLR7/8), and it is through a myd88-dependent pathway [59],

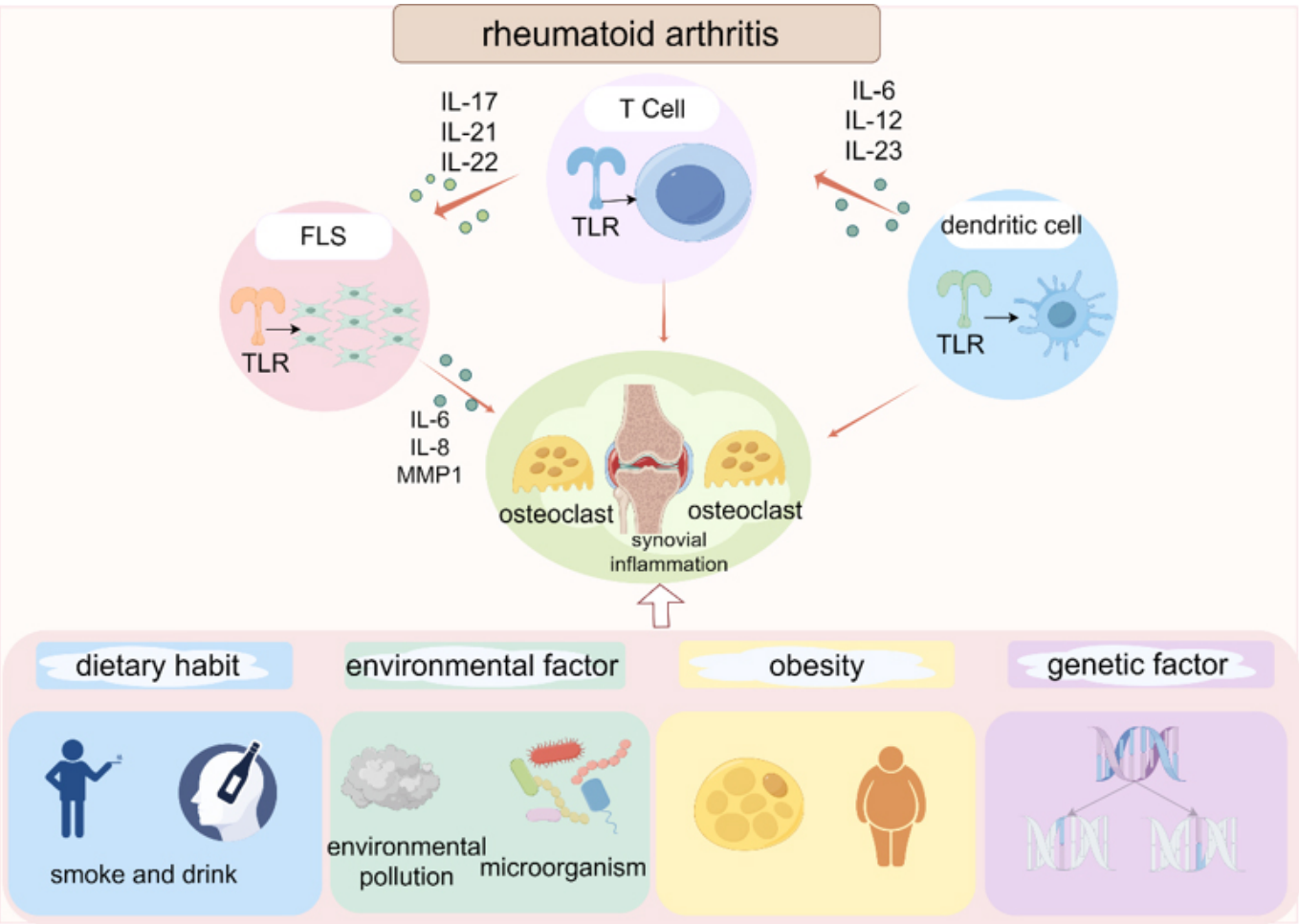

Fig. (2). Genetic factors and environmental factors such as smoking, alcohol consumption, diet, obesity, environmental pollution, etc., jointly influence and participate in the development of RA. DC, T cell, and FLS all express TLR receptors, which stimulate the release of inflammatory factors from immune cells through TLR activation, which ultimately leads to the generation of osteoclasts, resulting in joint loss. *(A higher resolution / colour version of this figure is available in the electronic copy of the article).*

IL-23 is critical for T cells to produce pathogenic IL-17 [60]. IL-17 produced by effector Th17 cells increases the expression of TLR2, TLR3 and TLR4 in RA-fibroblast-like synoviocytes (FLS) [61], which induces pro-inflammatory mediators such as cysteine-rich angiogenesis-inducing factor 61 (Cyr61), IL-23, and GM-CSF, which further exacerbate chronic inflammation, immune cell chemotaxis, synovial hyperplasia and joint destruction [62]. In addition, TLR-2, TLR-3, TLR-4, TLR-5, TLR-6, TLR-7, and TLR-9 are highly expressed in RA-FLS and are involved in the pathogenesis of RA [63]. For example, miR-19 aberrantly activates TLR-2 in RA-FLS and induces IL-6 and MMP3 production through the TLR-2 signaling pathway [64]. Poly (I: C) can stimulate TLR-3 to promote IL-8 and vascular endothelial growth factor (VEGF) production in FLS [65] as well as interferon-beta (IFN-β), C-X-C chemokine ligand-10 (CXCL10) [66]. Soluble CD14 can transmit inflammatory signals to FLS via TLR-4 to produce IL-6, IL-8, and others [67]. ST3GAL3 promotes the production of matrix metalloproteinase-1 (MMP1), MMP3, IL-6, and IL-8 through the TLR9/MyD88 signaling pathway [68]. RA-FLS also promotes the production of MMP1, MMP3, IL-6, and IL-8 through TLR-2, TLR-4 [69], and TLR-3 activate receptor activator of nuclear factor-kappa B ligand (RANKL), which promotes osteoclast formation and leads to inflammatory bone destruction [70].

In conclusion, it can be stated that DC, Th17 cells, FLS, IL-17, and IL-23 play a pivotal role in the pathogenesis of RA, namely synovial hyperplasia and bone and joint destruction. Furthermore, the connection of TLRs results in an immune response in the synovium that presents a vicious circle.

3.2. TLR and Systemic Lupus Erythematosus

Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies and the deposition of immune complexes, with a complex and varied clinical picture involving the skin [71], kidney

[72], central nervous system [73], cardiovascular system [74], gastrointestinal system [75] and other tissue systems. The kidneys are the most commonly involved target organ, and morbidity and mortality in SLE patients are mainly derived from lupus nephritis (LE) [76], of which approximately 30-60% in adults and up to 70% in children [77]. The etiology of SLE is complex, with genetic risk and environmental factors (air pollution, ultraviolet light, smoking, viral infections) [78] interact to lead to disease progression. The pathogenesis of SLE is not well defined, but it mainly involves T and B cell hyperfunction, IFN-I (especially IFN-α), and overproduction of proinflammatory cytokines [79]. Increasing evidence suggests that TLR receptors may be involved in the pathogenesis of SLE through a variety of pathways, including T and B cell activation, antibody production, and release of inflammatory factors. Recent studies have found that functional mutations in the TLR are also associated with the development of lupus in humans and mice, and a mutation in UNC93B1 (a transmembrane protein that acts as a regulator of the localization of TLR7 to the nuclear endosome) identified in a patient with childhood-onset lupus resulted in unrestricted recycling of TLR7 signaling and disruption of immune tolerance to nucleic acids. The importance of TLR signaling in lupus erythematosus is demonstrated [80]. Interferon is considered a key molecule in the pathogenesis of systemic lupus erythematosus (SLE). High levels of IFN-α are associated with up-regulated levels of anti-Ro52 and anti-La antibodies and inflammatory manifestations of the mucosal skin in SLE, and high levels of serum IFN-α are a significant genetic factor in SLE [81, 82]. TLR7 and TLR9 are strongly correlated with IFN-α expression and mediate signaling through MyD88 and IRAK4, leading to IFN-α production [83, 84]. Studies have shown that viral infections, particularly Epstein Barr virus (EBV), promote IFN-α secretion [85], and CPG-treated Peripheral blood mononuclear cells (PBMC) induced higher levels of IFN-α and TLR-9 gene expression compared to EBV-treated cells [86]. SLE TLR inhibitory peptide 1 can down-regulate IFN-α levels by inhibiting most of the downstream proteins of TLR7/9 in lupus animal models and SLE patients [87]. Another distinguishing feature of SLE is the large number of autoantibodies produced by self-reactive B cells, e.g., anti-dsDNA, anti-smith, anti-nuclear antigen (ANA), anti-ribonucleoprotein (RNP), anti-Ro, anti-La antibodies, etc [88, 89]. Anti-dsDNA antibody titers have been recognized as an important surrogate marker for assessing disease activity in SLE [90]. TLR7 can direct B cell activation and thus participate in antibody expression Fig. (**3**). Resting naïve B cells can generate Activated naïve (aNAV) B cells, double negative 2 (DN2) B cells, and DN2 cells in the presence of IL-21 via TLR7 and IFN-γ. DN2 cells also DN2 cells also differentiate into Antibody-secreting cells induced by TLR-7, IFN-γ, and IL-21, producing anti-Ro, anti-RNP, and anti-Smith antibodies. This is the pathway for activation of extrafollicular autoreactive antibody-secreting cells, a process that requires the involvement of TLR7, and in the absence of the elimination of the TLR7 ligand, R848 leads to a massive increase in cell death and a significant reduction in the frequency of differentiation [91]. In addition, Activated naïve (aNAV) B cells, under the dual stimulation of auto-antigen recognition by BCR and TLR7/TLR8, up-regulate cell-surface co-stimulatory molecules such as CD40, CD86, IL-21R, and HLA--DR, and transmit co-stimulatory signals to T cells, resulting in the polarization of T cells towards effector Th2 and Th17 cells, which in turn lead to differentiation of aNAV B cells into antibody-secreting cells (ASCs) in the presence of IL-21 and increased production of anti-DNA autoantibodies [92]. The germinal center (GC) is a major site for the production of high-affinity antibodies, and the GC reaction is another pathway by which B-cell activation leads to the formation of autoreactive antibody-secreting cells [93]. It was found that wild-type B cells can join existing GCs, clonally expand, persist, and contribute to autoantibody production and diversification through TLR7, B cell receptor specificity, antigen presentation, and IFN-I signaling [94]. It is suggested that TLR7 is also involved in autoantibody production in the GC.

To sum up, TLR7 and TLR9 are involved in the activation and differentiation of T and B cells, as well as the diversified production of autoantibodies, which exacerbates the pathogenesis of SLE.

3.3. TLR and Psoriasis

Psoriasis is a chronic inflammatory skin disease that typically presents clinically as well-defined silvery-white scales (white skin) and grey plaques (dark skin), the removal of which leads to small bleedings and the edges of which can move outwards, resulting in the covering of large areas of skin [95]. Psoriasis occurs on the scalp, limbs, trunk, and chest and is more prevalent in men than in women [96]. Psoriasis not only affects the skin but is often associated with other comorbidities such as arthritis, diabetes, non-alcoholic fatty liver disease, cardiovascular disease, and dry eye and uveitis involving the eyes [97-101]. Most people with psoriasis suffer substantial damage to their mental health, and psoriasis increases the risk of depression and suicide [102]. Several factors, including behavioral environmental, genetic, and immunological factors complicate psoriasis. Factors such as obesity [103], smoking and alcohol consumption [104], bacterial, fungal, and viral infections [105], and climate change [106] can act as triggers for the early onset of psoriasis and exacerbate the progression of psoriasis. About 40% of people with psoriasis or psoriatic arthritis have a family history of the disease, and most are female [107]. In addition, innate and adaptive immune cells are key factors in the pathogenesis of psoriasis. The typical pathological manifestation of psoriasis is the hyperproliferation of the epidermis, which is mainly triggered by innate immune cells through the release of cytokines that trigger psoriatic inflammation [108]. At the same time, the activated adaptive immune system also produces large amounts of inflammatory cytokines, creating a powerful inflammatory environment that drives the abnormal proliferation of keratinocytes, which, once activated, are highly proliferative and produce large amounts of chemokines, antimicrobial peptides, and other inflammatory mediators, exacerbating the inflammatory environment [109-111]. As shown in Fig. (**3**). The antimicrobial peptide

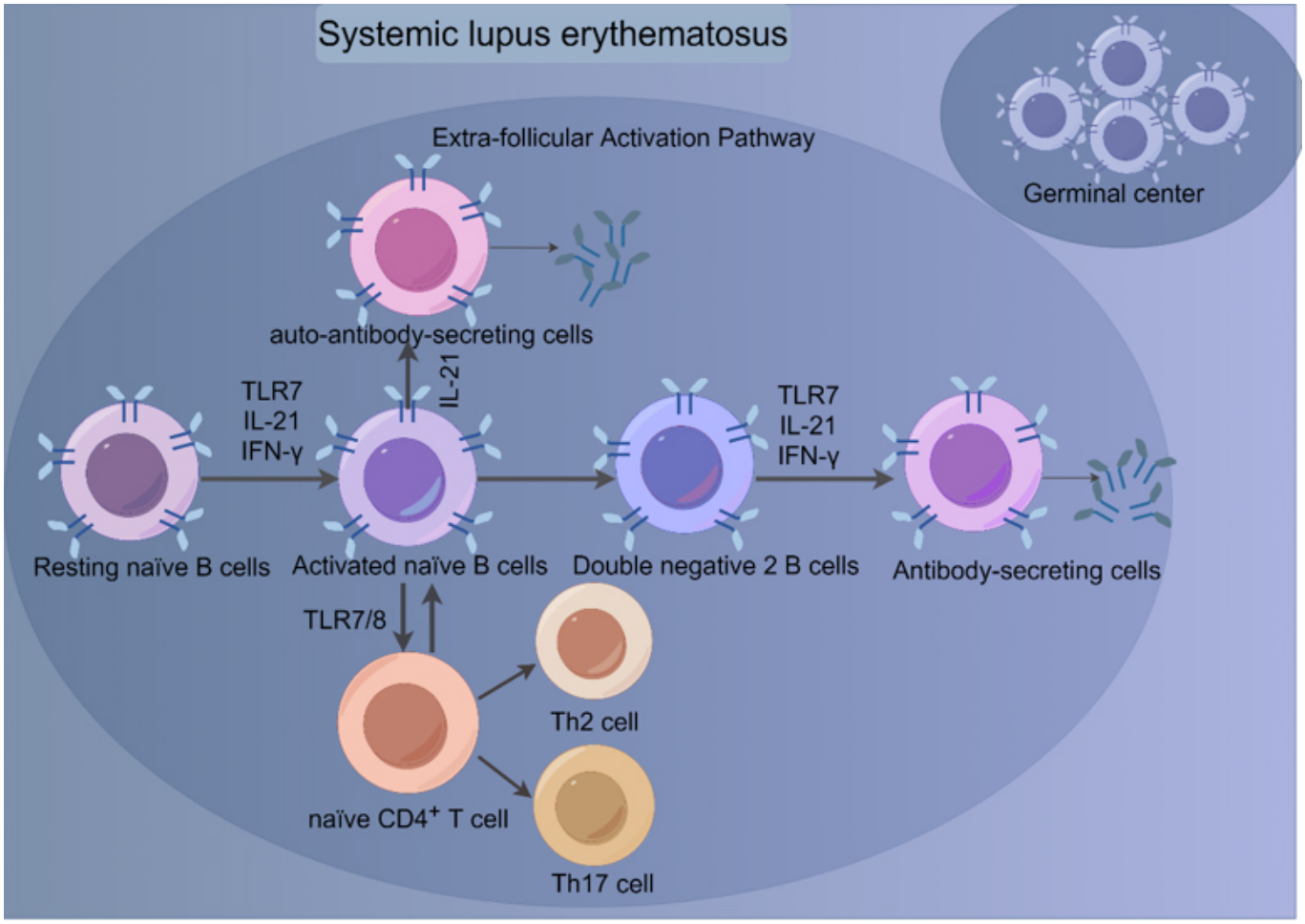

Fig. (3). SLE is significantly characterized by high levels of autoantibody production by autoreactive B cells, and TLR7 plays a key role by regulating the activation of autoreactive antibody-secreting cells and autoantibody production. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

LL37 has been implicated as a causative factor in psoriasis [112], and the LL37-DNA complex stimulates the production of IFN-β by pDCs via TLR9, whereas binding to RNA can stimulate the production of IFN-α by pDCs via TLR7, and additionally the RNA-LL37 complex activates the Monocyte-derived dendritic cells (MoDCs) via TLR8 and produces TNF-α and IL-6 and IL-12, IL-23 and IL-27 [113]. These cytokines (especially IL-12, and IL-23) enhance IFN-α-triggered monocyte-derived D promoting naïve T cell differentiation into Th1 and/or Th17 cells [114]. IL-17 produced by Th17 cells stimulates the proliferation of epidermal keratinocytes [115]. In addition, LL37 induces the production of TLR7/8, activates TLR8 in keratinocytes, and induces IL-17C by producing IL-36γ [116]. Functional expression of TLR2, TLR3, TLR4, TLR5, and TLR9 on keratinocytes induces keratinocytes to secrete cytokines and chemokines, such as TNF-a, CXCL8, CCL20, etc., when stimulated with the ligands, and the TLR3 and TLR9 ligands can also induce IFN-I [117, 118]. Phosphatidylglycerol was found to ameliorate psoriasiform lesions in an imiquimod (IMQ)-induced mouse model of psoriasis, suggesting that it could be a useful therapeutic [119]. Phosphatidylglycerol also restores the expression of inflammatory mediators to essentially controlled levels by inhibiting the activation of TLR2 and TLR4 under the PAMP [120] and the DAMP [121], which suppresses the expression of IL-1β, IL-6, and TNF-α in keratinocytes. In addition to inflammatory factors regulating the proliferation of keratinocytes, the positive and negative regulatory effects of miRNAs on keratinocytes have been gradually tapped [122]. miR-146a is a potent negative regulator of the innate immune response in keratinocytes. miR-146a reduces the expression of chemokines, cytokines, antimicrobial peptides, and signaling molecules through down-regulation of the IRAK1/TRAF6/NF-kB pathway upon stimulation with TLR2 ligands, thereby inhibiting the excessive inflammatory response in keratinocytes [123]. MicroRNA-181b [124], and miR-489-3p [125] can inhibit the TLR4 signaling pathway to suppress the proliferation of keratin-forming cells. This provides a new area for designing mechanism-driven therapeutic approaches from TLRs.

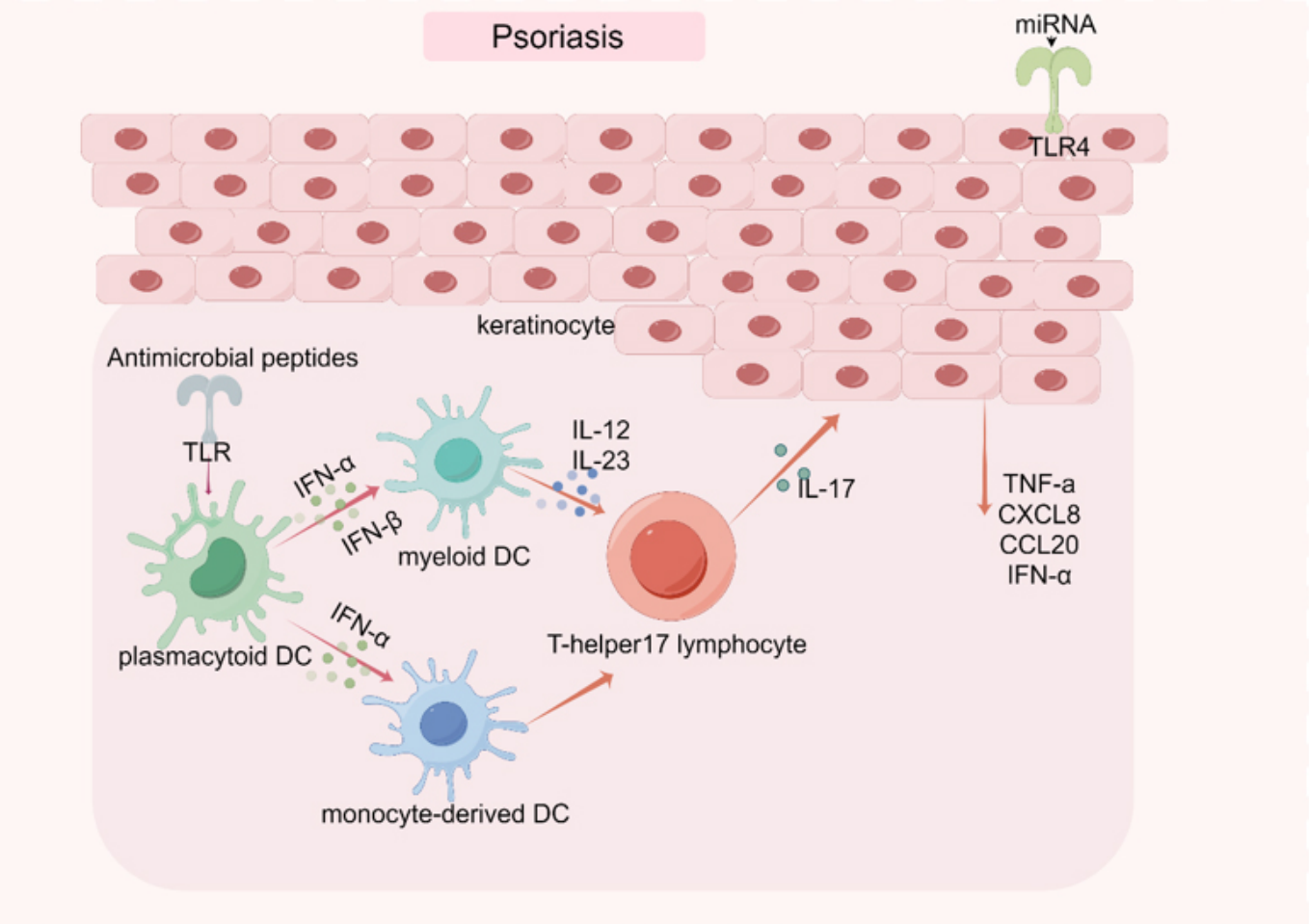

Fig. (4). Antimicrobial peptides stimulate IFN-I production by plasmacytoid dendritic cells, which leads to activation of myeloid dendritic cells and monocyte-derived dendritic cells, and activation of Th17 cells in response to cytokine coactivation, production of IL-17, which leads to the aberrant proliferation of keratinocytes. TLRs on keratinocytes, when stimulated by ligands, lead to the activation of keratinocytes and release of inflammatory factors, which exacerbate the abnormal proliferation. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

TLRs stimulate the activation of immune cells and keratinocytes, which induce a state of chronic inflammation in the epidermis and perpetuate the pathological alterations of the epidermis in a cyclical manner Fig. (**4**).

3.4. TLR and Sjögren Syndrome

Sjögren syndrome (SS) is a group of autoimmune disorders that primarily affect exocrine glands such as the salivary and lacrimal glands. The main symptom of desiccation syndrome is dryness of the eyes, mouth, pharynx, larynx, and/or vagina, in addition to which extra-glandular manifestations may also be present, including skin, musculoskeletal, pulmonary, renal, hematological, and neurological involvement [126]. SS is classified into primary Sjögren syndrome (pSS) and secondary Sjögren syndrome (sSS), depending on whether it is the first clinically manifested autoimmune disease or not [127]. The pathogenesis of SS is mainly reflected in the infiltration of salivary glands by intrinsic and adaptive immune cells and the presence of autoantibodies in the blood (especially anti-Sjögren's syndrome-related antigen A antibodies (anti-SAA) and anti-Sjögren syndrome-related antigen B antibodies (anti-SSB) [128]. An identification based on Cytometry by time-of-flight immunophenotyping found differences in peripheral blood levels of CD41 T and memory B lymphocytes, pDCs, activated HLA-DR1 CD4 and $CD8^{+}$T cells, and plasmablasts in pSS patients compared with control subjects. Cells, and plasmablasts, and in salivary gland biopsy specimens from patients with pSS, the presence of large numbers of activated $CD8^{+}$ T cells, terminally differentiated plasma cells, and activated epithelial cells [129]. Salivary gland epithelial cells (SGECs), mainly composed of follicular and ductal cells, are key to the initiation and propagation of the immune response and may activate the innate immune response and lead to an adaptive immune response to self-antigens when stimulated by triggering factors [130]. As shown in Fig. (**5**). SGECs achieve in-

nate immune function mainly through TLR receptor expression and cytokine secretion, while TLR2, TLR3, TLR4, TLR5, TLR7, and TLR9 [131-133] can be expressed in SGECs. TLR2, TLR3, and TLR4 induced different levels of intercellular adhesion molecule (ICAM)-1, CD40, B7-2, and MHC class I in SGECs from SS patients, suggesting a role for SS epithelial cells in the innate immune response [133]. TLR7 stimulates SS patient SGECs to facilitate Ro52-SS-A antigen presentation via MHC class I [134]. In addition, animal experiments revealed that TLR7 was significantly associated with salivary gland inflammation, and TLR7 was positively correlated with the levels of inflammatory markers CXCL13, CXCR5, TNF, and lymphotoxins (LT-α) [135]. Lysosomal-associated membrane protein 3 in salivary gland epithelial cells can amplify IFN-I production and induce ectopic TLR7 expression [136]. TLR2 activation is involved in the induction of IL-15 production by pSS SGECs and promotes inflammation through NF-κB activation [137]. A distinctive feature of SS patients is the ectopic presence of the mucin proteins MUC5B and MUC7 in the extracellular matrix of the salivary glands, and in-depth studies have revealed that the mucins can be recognized by TLR4 in the epithelium thereby inducing a significant elevation of CXCL8, TNF-a, IFN-a, IFN-β, IL-6, and IL-1b, which contributes to the development of the chronic state of SS [138]. In addition, dsDNA virus and Poly(I: C) stimulation of the TLR promotes B cell-activating factor (BAFF) production by SGECs [139]. Overexpression of BAFF enhances B-lymphocyte infiltration and also induces B-cell to GC B-cell differentiation [140], Thus, it plays a role in linking innate and adaptive immunity. At the border and inside the GC Tfh cells interact with B cells via ICOS and its ligand ICOSL, releasing large amounts of IL-21 to stimulate B cell activation as well as GC formation [141], involved in the pathogenesis of SS. Whereas endosomal TLR signaling can largely restore specific B-cell GC responses lacking IL-21R [142].

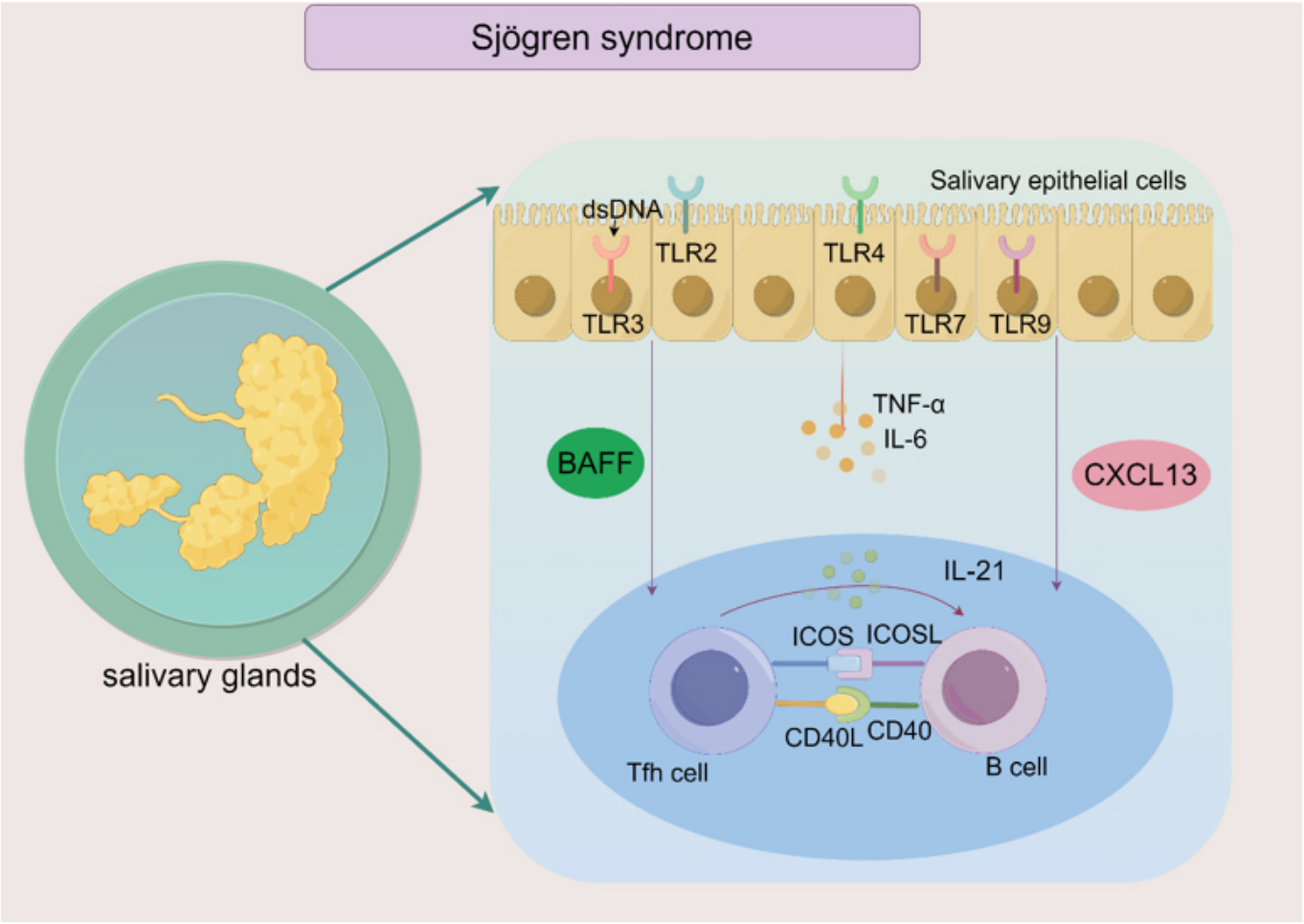

Fig. (5). Salivary glands are target organs for pSS, and SGECs play an active role in the pathogenesis of pSS by releasing inflammatory factors and presenting antigens through TLR receptors. SGECs also secrete BAFF via TLR in response to viral stimulation and promote B cell activation in concert with IL-21 and CXCL13. *(A higher resolution / colour version of this figure is available in the electronic copy of the article)*.

SGECs not only perform innate immune functions through TLR receptors but also activate adaptive immune cells, thereby exacerbating the chronic inflammation of salivary glands.

4. TLR AND TRADITIONAL CHINESE MEDICINE

Chinese medicines can activate and inhibit TLRs and also target innate and adaptive immune cells, suggesting that Chinese medicines can be involved in the activation and differentiation of immune cells and the production of cytokines related to immune response through the TLR signaling pathway Table **1**.

Celastrol is a triterpene constituent of the traditional Chinese herb tripterygium wilfordii with anti-inflammatory and antioxidant activity [143]. Celastrol regulates chronic inflammation and autoimmune diseases through multiple signaling pathways, including TLR, NF-κB, MAPK, etc [144]. The mechanism of action of Celastrol in the treatment of RA has been explained in various ways. Studies have shown that Celastrol can inhibit LPS-stimulated FLS migration and invasion by inhibiting MMP-9 expression and activity by inhibiting the TLR4/MyD88/NF-kB pathway [145].In addition, in rats with collagen-induced arthritis, Celastrol can inhibit RA-induced autophagy in cardiomyocytes by inhibiting the TLR2/HMGB1 pathway, thus exerting cardioprotective effects [146].

Caulis Sinomenii has various pharmacological effects such as anti-inflammatory, analgesic, immunosuppressive, anti-tumor, hepatoprotective, and antioxidant effects [147]. Sinomenine is the principal ingredient extracted from the Caulis Sinomenii. A parallel randomised controlled trial demonstrated that sinomenine in combination with methotrexate can enhance the disease activity of patients with RA while concurrently reducing the incidence of gastrointestinal adverse reactions and hepatotoxicity. These findings suggest that sinomenine may be a viable option for incorporation into combined therapeutic regimens [148]. Furthermore, its mechanism of action has been the subject of extensive investigation.The in vitro culture of RA-FLS demonstrated that Sinomenine inhibited the proliferation of FLS and prevented cartilage destruction [149]. In addition, Sinomenine also exerts anti-inflammatory effects on IL-1β-induced human RA-FLS by inhibiting the TLR4/MyD88/NF-κB signaling pathway and can inhibit the expression of NO, PGE2, iNOS, and COX-2 [150]. In lipopolysaccharide-induced macrophage immune response, Sinomenine down-regulates the levels of inflammatory factors TNF-α, IL-1β, and IL-6 via the TLR4/MyD88/NF-κB pathway [151]. The results of these studies indicate that Sinomenine exerts its anti-inflammatory and immunosuppressive effects through TLR signalling, thereby eliciting therapeutic outcomes.

Artemisinin is isolated from the Chinese herb Artemisia annua L, which is commonly used as an active ingredient in the fight against malaria. Artemisinin and its derivatives can play a therapeutic role in a wide range of diseases, including cancer, viral diseases, inflammation, and autoimmune disorders, and they have been widely exploited [152]. Dihydroartemisinin (DHA), a derivative of artemisinin, has been found to inhibit the proliferation of splenocytes via the TLR4/IRF/IFN pathway in isolated splenocytes from MRL/lpr mice with a predisposition to lupus erythematosus, suggesting that DHA can be a treatment for SLE via the TLR [153]. To improve the efficacy of DHA, a co-administration system of DHA and HMGB1 siRNA was established and found to significantly reduce TLR4 expression and subsequent MyD88, IRAK4, and NF-κB, implying that DHA can treat TLR4-mediated lupus erythematosus nephritis [154]. Another in-depth study revealed that the TAT-CLs-DHA/siRNA system could inhibit the proliferation and activation of B cells through the TLR4 signaling pathway, providing a new target for the treatment of SLE through the TLR4 signaling pathway [155].

Curcumin is a phenolic constituent extracted from the traditional Chinese medicine Curcuma longa L. It has a broad spectrum of medicinal functions, including anti-inflammatory, anti-angiogenic, anti-diabetic, antibacterial, and anti-tumor properties [156-158]. A meta-analysis shows good clinical efficacy of curcumin in the treatment of psoriasis [159]. In examining the mechanism of action of curcumin, it was determined that TLR represents a crucial target. The main TLR families involved are TLR2 [160], TLR4, TLR5 [161], TLR9 [162]. In vitro culture of mouse bone marrow-derived macrophage revealed that curcumin exerts ameliorative effects on SLE by inhibiting cell activation and BAFF production in response to TLR4 stimulation [163].In the propranolol-induced rat psoriasis model, curcumin was observed to reduce the expression of TLR and immune factors significantly, thereby indicating that curcumin may exert an ameliorative effect on psoriasis through TLR [164].

Table 1. Application of Chinese herbal medicine active ingredients in intervening autoimmune diseases through TLR family-related proteins.

Active Ingredient	Traditional Chinese medicine	TLR	Autoimmune Disease	References
Celastrol	Tripterygium wilfordii	TLR2, TLR4	rheumatoid arthritis	[145] [146]
Sinomenine	Caulis Sinomenii	TLR4	rheumatoid arthritis	[151]
Dihydroartemisinin	Artemisia annua L	TLR4	systemic lupus erythematosus	[153]
Curcumin	Curcuma longa L	TLR2, TLR4	psoriasis	[163]
Baicalin	Scutellaria baicalensis Georgi	TLR7/8	psoriasis	[167]
Total glucosides of paeony	Paeoniae Radix Alba	TLR4	rheumatoid arthritis	[172-174]

Baicalin is one of the most representative components of the traditional Chinese medicine Scutellaria baicalensis Georgi [165]. Baicalin contains a variety of pharmacological effects such as antioxidant, anticancer, anti-inflammatory, antibacterial, cardioprotective, hepatoprotective, nephroprotective, and neuroprotective properties [166]. Studies have shown that baicalin has a significant inhibitory effect on IMQ-induced psoriasis-like skin inflammation by inhibiting γδ T-cell activation and the production of IL-17a, IL- 22, and IL-23. IMQ is an agonist of TLR7/8 and a potent immunostimulant used in the induction and exacerbation of psoriasis via the IL-23/IL-17 axis [167]. Suggesting TLR as a potential target for baicalin in the treatment of psoriasis.

Total glucosides of paeony (TGP), the herbal active substance of the Chinese medicine Paeoniae Radix Alba, has been found to have therapeutic effects on a wide range of autoimmune diseases, such as RA [168], SLE [169], psoriasis [170], SS [171]. TGP plays a role in the treatment of rheumatoid arthritis by inhibiting synoviocyte proliferation, lymphocyte proliferation, and the release of inflammatory factors [172]. In a complete Freund's adjuvant-induced arthritis model, TGP significantly alleviated foot-plantar swelling and synovial injury and reduced TLR2, TFAR6, and NF-κB levels in rats, suggesting that TGP exerts an ameliorative effect on inflammation through the TLR2/TRAF6/NF-κB pathway [173, 174].

CONCLUSION

TLRs are widely distributed in immune cells such as dendritic cells, T and B lymphocytes, and non-immune cells such as fibroblasts and keratinocytes. It is essential for the regulation of autoimmune diseases by linking innate and adaptive immune responses that can be activated by specific exogenous substances (e.g., bacterial LPS, lipopeptides, lipoproteins) as well as by endogenous substances (e.g., viral DNA, RNA, and HMGB1 and LL37, etc.). Intensive studies of the TLR receptor have revealed that it can be involved in immune cell activation, differentiation, and cytokine production through the NF-KB, MAPK, and IFN signaling pathways, thereby exacerbating inflammation in autoimmune diseases. In addition, TLR-targeted therapy is a promising focus for further research on autoimmune disease. For example, IRAK-4 inhibition can lead to significant suppression of TLR responses in DCs, keratinocytes, and T cells and already has potential for preclinical evaluation in a variety of inflammatory and immune-related disorders, including, but not limited to, e.g., rheumatoid arthritis, psoriasis. TLR4, as a widely studied TLR, has also been intensively investigated for its inhibitors, and the utilization of natural product agents in particular, may provide new ideas for the development of new drugs.

We also noticed that TLR also plays a role in the treatment of autoimmune diseases through active ingredients of traditional Chinese medicines. This study revealed that active ingredients of traditional Chinese medication exerted therapeutic effects through anti-inflammation and immunosuppression. Still, due to fewer references, the underlying mechanisms need to be further investigated. Due to the multi-component and multi-target characteristics of TCM components, some of them may be potential agonists or inhibitors of TLR and have greater potential for drug development in the treatment of autoimmune diseases.

LIST OF ABBREVIATIONS

TLR	=	Toll-Like Receptor
RA	=	Rheumatoid Arthritis
SLE	=	Systemic Lupus Erythematosus
SS	=	Sjögren's Syndrome
PAMP	=	pathogen-Associated Molecular Pattern
DAMP	=	Damage-Associated Molecular Pattern
LPS	=	Lipopolysaccharide
HSP	=	Heat Shock Protein
HMGB1	=	High Mobility Group Box-1
TNF-α	=	Tumor Necrosis Factor-Alpha
GM-CSF	=	Granulocyte-Macrophage Colony Stimulating Factor
CXCR5	=	C-X-C Chemokine Receptor Type 5
ICOS	=	Inducible Costimulatory Molecule
VEGF	=	Vascular Endothelial Growth Factor
CXCL10	=	C-X-C Motif Chemokine Ligand 10
MMP1	=	Matrix Metalloproteinase-1
RANKL	=	Receptor Activator of Nuclear Factor-Kappa B Ligand
ASCs	=	Antibody-Secreting Cells
GC	=	Germinal Center
SGECs	=	Salivary Gland Epithelial Cells
BAFF	=	B cell-Activating Factor

DECLARATIONS

Figures were created by Figdraw (www.figdraw.com).

AUTHORS' CONTRIBUTIONS

Yaru Wang: collected the data and drafted the manuscript. Hui Liu and Xintian Tang collected the data and drafted the manuscript. Mingying Liu drew tables and figures. Lin Bao revised the manuscript. Xiaodong Liang revised the manuscript and is accountable for the accuracy or integrity of the work. All authors read and approved the final manuscript. Yifan Liu: are accountable for the accuracy or integrity of the work. All authors read and approved the final manuscript.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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