Review

Toll-like receptor pathways in autoimmune diseases

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Abstract

Autoimmune diseases are a family of chronic systemic inflammatory disorders, characterized by the dysregulation of the immune system which finally results in the break of tolerance to self-antigen. Several studies suggest that Toll-like receptors (TLRs) play an essential role in the pathogenesis of autoimmune diseases. TLRs belong to the family of pattern recognition receptors (PRRs) that recognize a wide range of pathogen-associated molecular patterns (PAMPs). TLRs are type I transmembrane proteins and located on various cellular membranes. Two main groups have been classified based on their location； the extracelluar group referred to the ones located on the plasma membrane while the intracellular group all located in endosomal compartments responsible for the recognition of nucleic acids. They are released by the host cells and trigger various intracellular pathways which results in the production of proinflammatory cytokines, chemokines, as well as the expression of co-stimulatory molecules to protect against invading microorganisms. Particular, TLR pathway-associated proteins, such as IRAK, TRAF, and SOCS are often dysregulated in this group of diseases. TLR-associated gene expression profile analysis together with single nucleotide polymorphism (SNP) assessment could be important to explain the pathomechanism driving autoimmune diseases. In this review, we summarize recent findings on TLR pathways regulation in various autoimmune diseases, including Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), systemic sclerosis (SSc), and psoriasis.

KEYWORDS:

Toll-like receptors (TLRs); autoimmune disease; IL-1 receptor associated kinase (IRAK); TNF receptor associated factor (TRAF); Suppressor of cytokine signaling (SOCS)

Autoimmune diseases are characterized by the dysregulation of the immune system which finally results in the break of tolerance to self-antigen. Even though the accurate etiology and pathogenesis of the majority of these diseases are still not clear, complex elements, including genetic, environmental, hormonal factors may provoke the autoimmune processes leading to the development of the disease. Concerning the role of derailed immune responses in the pathogenesis, aberrant processes both in the innate and adaptive immune system have been shown to participate in the disease initiation and perpetuation [1]. Within these processes, numerous studies have been demonstrated that Toll-like receptors (TLRs) have an essential role in various autoimmune diseases, including Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), multiple sclerosis (MS), rheumatoid arthritis (RA), systemic sclerosis (SSc), and psoriasis. [2, 3].

Toll-like receptors

The innate immune system is the first line of host defense mechanisms against invading microorganisms and forms the basis of the development of adaptive immunity. Host cells express diverse pattern recognition receptors (PRRs) include toll-like receptors (TLRs), C-type lectin-like receptors (CLRs), Retinoic acid-inducible gene (RIG)-I-like-receptors (RLRs), and Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs). These can recognize a wide range of pathogen-associated molecular patterns (PAMPs). These mechanisms trigger the intracellular signaling pathways, which results in releasing of proinflammatory cytokines, chemokines, and interferons (IFNs), as well as lead to the expression of co-stimulatory molecules [4].

TLRs are the most characterized PRRs, which are capable of potently activating different cell types, which could be highly expressed on most immune cells, as well as other cell types, including chondrocytes, endothelial cells and fibroblasts [5]. Their downstream signaling pathways lead to the

production of a wide range of immune-stimulatory cytokines and chemokines [6]. Aberrant activation of TLRs may result in unrestricted inflammatory responses therefore the family of TLRs may play a pivotal role in the development of autoimmune diseases.

Ten TLR subtypes have been identified in humans during the last decade. All of them have their specific ligands, expression profiles and cellular localization. TLRs belong to the type I transmembrane proteins, which are composed of a transmembrane domain, an amino-terminal ectodomain responsible for PAMPs recognition, and a cytoplasmic carboxy-terminal toll interleukin-1 receptor (IL-1R) homology (TIR) domain [7, 8].

Among those, TLR1, TLR2, TLR4, TLR5, TLR6 and TLR10 are generally regarded as extracellular receptors. Since TLR2 addressed as heterodimer in combination with TLR1 or TLR6, while TLR10 was indicated as originating from the TLR1/TLR6 precursor, they all function as heterodimeric receptors and recognize components of microbial cell walls and membranes including peptidoglycans and lipopeptides. TLR4 can recognize lipopolysaccharides (LPSs), specific for gram-negative bacteria. On the other hand, TLR5 also resides in plasma membranes and engage flagellin, a specific component for flagellated bacteria [9–11].

The family of TLR3, TLR7, TLR8 and TLR9 are intracellular receptors located in endosomal compartments and responsible for the recognition of nucleic acids derived from viruses, bacteria and the host. Double stranded RNA (dsRNA) activates TLR3, while TLR7 and TLR8 recognize single stranded RNA (ssRNA). More specifically, TLR9 recognizes unmethylated CpG DNA [9–11].

As mentioned before, the TLRs differ in their expression pattern within various cell types. Their signal transduction pathways also have different mechanisms [12]. Two main adaptor pathways observed in TLRs signaling transduction, namely the myeloid differentiation primary response 88 (MyD88) and

TIR-domain-containing adaptor inducing interferon (IFN)-β (TRIF, also known as TICAM1) pathway. MyD88 as an adaptor protein could bind directly to the cytosolic domain and lead to induction of gene expression via the transcription factors nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activating protein (AP)-1 or interferon-response factor (IRF)-1, 5 and 7. On the other hand, TRIF basically transmits the signal downstream and leads to activation of IRF 3 mainly together with NF-κB [13–17].

TLR3 is the only TLR that exclusively uses the TRIF-dependent pathways, whereas the other TLRs are restricted to the MyD88-dependent pathway. Exceptionally, TLR4 activates both pathways by first leads to activation of the MyD88 pathway at the plasma membrane then activates the TRIF-pathway via TRIF-related adaptor molecule (TRAM) at the endosomes [11, 18, 19]. TLR4 was the first identified human TLR. TLR4 has been implicated in the recognition of viral structural and non-structural proteins, which leads to the production of a wide range of immune-stimulatory cytokines and chemokines [6, 20, 21]. Figure 1 summarized the function and signalization of TLRs. Table 1 gave the brief summary of the TLR family.

IL-1 receptor associated kinase (IRAK) family harbors the TIR domain of TLRs. It was originally regarded as the serine/threonine kinase associated with the IL-1 receptor [22]. IRAK1, IRAK2, IRAK-M, and IRAK4 have been identified so far. Among those, IRAK1 and IRAK4 are two active kinases since they could harbor a critical aspartate residue, while this residue is not conserved in the other two members of IRAK, so-called inactive ones. IRAK proteins consist of a central kinase domain and an N-terminal ligand domain which mediates activation of MyD88. As the result of two kinase pathways, NF-κB together with mitogen-activated protein kinase (MAPK) pathways can be activated.

Moreover, IRAK1 may play a role in tumor necrosis factor receptor (TNFR) superfamily-induced signaling pathways, as well [23].

MyD88 interacts with a cytoplasmic carboxy-terminal TIR domain of TLRs to recruit IRAK1 and IRAK4 upon stimulation. IRAK1 is further phosphorylated by the IRAK4 activation. Activated IRAK1 subsequently binds to the TRAF domain of TNF-receptor associated factor (TRAF) 6. The IRAK1/TRAF6 complex activates another complex which consists of the TGF-β-activated kinase 1(TAK1) and TAK1-binding proteins including TAB1, TAB2 and TAB3. Phosphorylation of the inhibitor of κB kinase (IKK) complex composed of IKK-α, IKK-β and NEMO/IKK-γ and MAPK kinase 6 (MKK6) is induced by TAK1, and thereby induces the activation of NF-κB and MAPK [24, 25].

Another proinflammatory cytokine, TNF-α, functions as a major mediator of apoptosis as well as immunity and inflammation, transduces its signals by binding with TNF receptors (TNFR-I and TNFR-II). The role of TNFR-II phosphorylation on its signaling properties is less understood than that of TNFR-I. TNFR-I takes most responsibility of TNF-α signaling when the death domain interacts with the death domain-containing adaptor proteins such as TNFR associated death domain (TRADD). Upon TRADD binding to the TNFR-I, it may lead to the recruitment of receptor interacting protein (RIP) and TRAF2 in separate manner for NF-κB activation for the cell-protective pathway. While the recruitment of the complex of TRADD and Fas-associated death domain (FADD) results in programmed cell death [26]. On the other hand, TNFR-II does not contain this death domain in the cytoplasmic tail. The intracellular domain of TNFR-II contains a consensus motif that allows binding to TRAF2 directly [27–29].

The TRAF proteins are composed of 4 domains, which include the multiple zinc finger repeats (TRAF Zn-finger) that are involved in effector functions (essential for the activation of downstream signaling cascades), an amino-terminal really interesting new gene (RING)-finger, the N-terminal (TRAF-N) coiled-coil domains and the C-terminal (TRAF-C) domains [30].

In comparison with other TRAFs, TRAF6 has the most divergent TRAF-C domain and shows the least homology to the prototypical TRAF domain sequence [31]. There are distinct differences in peptide binding to TRAF6 and to the other TRAFs due to the special structure of TRAF6. Therefore, TRAF6 has its unique biological function. TRAF6 is a convergence point for both upstream and downstream signaling cascades. It regulates a variety of physiologic processes, including both innate and adaptive immunity, bone metabolism, cell proliferation together with differentiation and many others [32]. Unlike other TRAFs, which only mediate signaling from the TNFR superfamily, TRAF6 also participates in the signal transduction of IL-1R/TLRs to activate inflammatory and apoptotic signaling pathways [33, 34].

Suppressor of cytokine signaling (SOCS) 1 was first identified and reported by three research groups with different methods in 1997. From then on, SOCS family set an important insight into the unelucidated mechanism of cytokine signaling. SOCS 1 is also known as JAK-binding protein (JAB) or STAT-induced STAT inhibitor (SSI) 1 [35–37]. The SOCS family contains eight protein members, which are cytokine-inducible Src homology 2 (SH2) protein (CIS), SOCS1, SOCS2, SOCS3, SOCS4, SOCS5, SOCS6 and SOCS7. They all have a central SH2 domain, an amino-terminal domain of variable length and sequence, and the SOCS box which has a segment with a carboxy-terminal 40 amino acids. Activation of the intracellular molecules, including Janus family kinases (JAKs) and

signal transducers and activators of transcription (STATs), is essential for the cytokine signaling [35–37].

The SOCS family of proteins is regarded as key participants of the negative feedback loop that regulates the intensity, duration and quality of immune cytokine signaling. Among the others, SOCS1 is one of the best characterized family members which is one of the multiple targets of miR-155. We have previously shown the expression pattern of miR-155 as well as the gene expression of SOCS1 in SS patients. (unpublished data)

Cytokines such as IFN-γ, TNF-α, together with IL-4 up-regulate the gene expression of CIS, SOCS1, SOCS2 and SOCS3 mRNA. SOCS1 is also functioning as an inhibitor of the LPS-activated TLR signaling pathway through directly blocking IRAK1 and IRAK-4 [7, 38]. MyD88-adaptor like (Mal) is regarded as bridge for interacting with MyD88 of TLR2 and TLR4 signaling. SH2 domain of SOCS1 could recognize phosphorylated Mal and induce polyubiquitination and subsequent proteasomal degradation [39].

Targeted proteins and pathways of Toll-like receptors are summarized in Figure 2.

Table 2 summarized the structure of IRAK, TRAF and SOCS family protein.

Primary Sjögren's syndrome

Sjögren's syndrome (SS) is a slowly progressive systemic autoimmune inflammatory disease that primarily affects middle-aged women (female to male ratio: 9:1), although it may be found in all ages including childhood. The target organs are salivary and lachrymal glands. Therefore, patients show symptoms of dry mouth and dry eyes [40]. Beside the pathognomonic glandular symptoms (GS), other systemic symptoms, denoted as extraglandular manifestations (EGMs), also found in approximately

one third of the patients. These patients frequently complain about fatigue, Raynaud's phenomenon, muscle and joint pain [41].

The expression profile of various TLRs is quite different in primary SS patients compared to that of healthy individuals [42]. Cultured salivary gland epithelial cells (SGECs) have been shown to express functional TLR2, TLR3 and TLR4 following treatment with their respective ligands. The TLR1, TLR2 and TLR4 mRNAs are significantly over-expressed in primary SS SGECs compared to controls [42, 43]. The expression level of TLR2, TLR3 TLR4 and MyD88 is higher in the labial salivary glands of SS patients compared to controls. Therefore it is informative to assess them in different salivary gland cell types, including acinar cells, infiltrating mononuclear cells and ductal epithelial cells. The TLR expression level showed similar pattern in all types of human salivary gland cells [44]. As mentioned before, peptidoglycans could activate TLR2, which has been indicated to induce the production of interleukins such as IL-17 and IL-23 in the peripheral blood mononuclear cells (PBMCs) of SS patients via IL-6, signal transducer and activator of transcription (STAT) 3 and NF-κB pathways [45].

We reported previously the concurrent over-expression of miRNA-146 and TRAF6 gene in primary SS patients compared to controls [46]. The over-expression of TRAF6 is surprising since miR-146a could inhibit the expression of TRAF6 [47]. In the same patient pool, we could demonstrate a similar pattern with the concurrent enhanced expression of miRNA-155 and SOCS1. In both cases the over-expression of TRAF6 and SOCS1 was related to the levels of miRNA-s. These phenomena may be explained by the following possible reasons: a.) existence of chronic persisting EBV infections; b.) the function of TRAF6 and SOCS1 might be complemented by other TRAF and SOCS molecules and signaling factors; c.) miR-146a and miR-146b are not the only miRNAs which targets TRAF6 protein whereas miR-155 is also not the only miRNA which targets SOCS1 protein.

Previously we have assessed circulating cytokines in primary SS patients compared to healthy controls and found amongst others that serum interleukin-10 level was significantly decreased in primary SS patients [48]. The impaired IL-10 signaling might be associated with SOCS1 induction. Overexpression of SOCS1 in primary SS could be correlated to these results.

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is the most prevalent systemic autoimmune disease which has a large spectrum of clinical presentations since SLE can affect multiple organs, including skin, joints, kidneys, lungs, nervous system, and serous membranes. Its diversity of clinical features is matched by the complexity of the pathogenetic factors including genetic, hormonal, and environmental factors [49]. Human plasmacytoid dendritic cells (pDCs) regarded as critical elements involved in the pathogenesis of autoimmune diseases [50]. They can produce cytokines and chemokines in response to autoimmune complexes including self DNA and small nuclear ribonucleoprotein particles (snRNPs) in SLE through a cooperative interaction between TLRs and Fc-γ receptors (Fc-γ-Rs) [51, 52]. Both TLR7 and TLR9 are associated with the stimulation of B cells and the production of IFN-α in SLE. TLR7 shown higher expression level on human pDCs compared with the other RNA-activated endosomal TLRs, TLR3 or TLR8 [51]. TLR7 binding with U1 snRNP mediated by Fc-γ-Rs results in a massive release of IFN-α [51]. TLR7 antagonists could inhibit IFN-α production by pDCs in response to nucleic acid-containing immune complexes [52, 53]. On the other hand, it is also believed that the production of type I IFN (i.e. IFN-α and IFN-β) and TNF-α in SLE is highly related with TLR9 [53]. The immune complexes derived from serum of SLE patient are translocated to the endosome for activating TLR7 or TLR9, resulting in dimerization and internalization leads to IFN-α or TNF-α

secretion. Increased levels of IFN-α in serum and higher expression level of IFN-inducible genes in PBMCs extracted from SLE patients have been suggested to be responsible for severe stage of disease activity [54, 55]. Activation of TLR9 through transcription factor IRF7 which is activated by the adaptor MyD88 leads to high level of IFN induction. The MyD88/IRF7 complex together with A/D-type CpG oligodeoxynucleotide (CpG-A, an IFN-inducing TLR9 ligand) are normally retained in the endosome of pDCs. CpG-A is rapidly transferred to lysosome when in conventional dendritic cells induces the production of type I IFN [56]. During immune stimulation uridine-rich RNAs are recognized by pDCs via TLR7, while human monocytes and myeloid DCs through TLR8 [51]. Myeloid DCs respond to TLR7/8 ligands via Fc-γ-Rs, which leads to the production of IL-12 and the induction of T helper type 1 (Th1) cell proliferation [57].

Interferon, TNFs and specific interleukins are induced by TLRs. For instance, the expression of TNF-α, IL-6 and IL-23, IL-10 is induced by TLR4 activation [58]. TLRs are activated in response to accumulation of apoptotic bodies. TLRs 7 and 9 expression levels were significantly increased in African American and European American lupus patients compared to age-matched controls. Serum levels showed significant increase in expression of IL-6, INF-α, IFN-γ and TNF-α in lupus patients compared to healthy individuals [59].

The TLR4 polymorphism has not been found to be associated with the susceptibility to SLE so far. The Mal protein, also known as the TIR domain-containing adaptor protein (TIRAP), is implied to have a role in modulating intracellular signaling triggered by the MyD88-dependent TLR2 and TLR4. The Leu180 allele of MAL/TIRAP polymorphism indicated reduced susceptibility to SLE regarded as a protective factor against the development of SLE [60] .

The single nucleotide polymorphisms (SNPs) of TLR7 rs3853839, TLR8 rs3764880, together with TLR9 rs351240 have been shown to increase the risk of SLE in an Asian population [61, 62]. Moreover, the SNPs of TLR9 rs352139 and rs351240 are associated with lupus nephritis [63]. In a Danish population, the SNPs of TLR3 rs3775291, TLR8 rs3764879, TLR9 rs352143 all showed association with SLE. The mRNA expression levels of TLR7 and TLR8 also significantly higher in SLE patients than in healthy controls [64]. These results indicate that genetic variations of certain TLR gene expression are implicated in the pathogenesis of the disease, which together associate with SLE susceptibility and clinical phenotype development.

The polymorphisms (rs11465955, rs1624395, rs1152888 and rs1370128) of IRAK-M in 2033 SLE patients compared with 2357 healthy controls from four independent European-descent populations (Spain, Germany, Italy and Argentina) were checked previously. The SNP rs1152888 of IRAK-M was not associated with SLE in this populations, while the other three showed differences between patients and controls [65].

However, the expression and pathophysiological role of TNF adapters in SLE have been poorly understood so far. Zhu L et al. found that the expression of mRNA for TNF adapter molecules TRADD protein, FADD protein, RIP, and TRAF2 decreased significantly in PBMCs from patients with SLE. Moreover the expression of these adapters were negatively correlated with the SLE disease activity index (SLEDAI). These abnormalities may be involved in the immunopathogenic injury mediated by the aberration TNF-α signaling pathway in SLE [66].

Being expressed in immune cells, suppressors of cytokine signaling proteins, CIS, SOCS1, SOCS2 and SOCS3, can regulate cytokine signaling and immune responses. To evaluate the possible expressional dysregulation of CIS, SOCS1, SOCS2 and SOCS3 in SLE and RA patients, the transcript levels of

these genes in PBMCs from SLE and RA patients were determined and statistically compared with those in PBMCs from healthy individuals. SLE patients with active disease significantly express higher CIS transcript levels than normal individuals and SLE patients with inactive disease, whereas the difference in SOCS1, SOCS2 and SOCS3 transcript levels between normal individuals and SLE patients are not statistically significant. These data suggest that CIS can serve as an SLE disease marker and may be involved in the pathogenesis of SLE, and that TNF-α may play an important role in the regulation of CIS and SOCS2 gene expression in PBMCs *in vivo* [67]. In monocytes higher expression level of STAT1 proteins was shown from SLE patients compared to controls, which also positively correlated with SLEDAI. The expressions of phospho-STAT1 protein and SOCS1 gene in the skin lesion from patients with SLE were both up-regulated compared with normal skin tissue from healthy controls. In conclusion, the JAK-STAT1 signaling pathway was hyperactivated while SOCS1 was down-regulation in skin lesions and monocytes of Asian SLE patients [68].

Additionally, TLR2 and TLR4 could be necessary for the initiation of antiphospholipid antibodies production and activation of the endothelium, resulting in thrombosis development in the pathogenesis of antiphospholipid syndrome secondary to SLE [69].

Multiple sclerosis

Multiple sclerosis (MS) is an autoimmune neurological disease which affects the brain and the spinal cord leads to a main triad symptoms of inflammation, demyelination and gliosis. MS is causing the nerve signals to slow down or even stop due to damaged or lack of the protective covering of myelin sheath surrounding the nerve cells, resulting in single or multiple symptoms including motor

disabilities, speech disabilities, swallowing disabilities, visual disabilities and other neuronal problems. [70]

The activation of the transcription factor NF-κB may be implied in the microglial response to myelin damage in MS lesions. Up-regulation of NF-κB controled adhesion molecules and cytokines result in enhancement of the inflammatory reaction [71]. After stimulation with TLR ligands and cytokines that induce NF-κB, the expression of NF-κB DNA-binding activity was elevated in macrophages of MS patients [72].

TLR ligands have also been identified as T-cell promoter of MS [73]. TLRs have diverse roles in forming of axonal path, dorso-ventral patterning together with cell-fate determination. Specifically, TLR2 and TLR4 differentially modulate adult hippocampal neurogenesis through unknown ligands [74]. TLR ligands can inhibit the differentiation of several cell types; TLR2 ligands can suppress the process that the mesenchymal stem cells differentiated into osteogenic, adipogenic, and chondrogenic cells [75]. The expression of TLR2 observed on oligodendrocytes, while higher expression of TLR2 in MS lesions. Hyaluronan receptor is capable of inhibiting the maturation and remyelination oligodendrocyte precursor cells (OPCs) via TLR2 [76]. TLR2 also associated with the high levels of hyaluronan found in the areas of complete demyelination in MS. Altered TLR2 activation results in the dysfunction of hyaluronan synthesis and degradation on oligodendrocytes, which may imply the adequate remyelination blockade [77]. TLR9 was identified in B cells and pDCs [78]. Human TLR9 is only found on pDCs and is able to recognize viral DNA within the early endosomes at the initial phase of viral infections since TLR9 recognizes unmethylated CpGDNA [79]. Both TLR2 and TLR9 has been associated with the response to several human viral infections, including cytomegalovirus, hepatitis C, EBV, varicella zoster virus and herpes simplex viruses types 1 and 2 (HSV) [80–82].

Activation of TLR2 induces the production of proinflammatory cytokines, including IL-6, IL- 8, and TNF-α. Moreover, TLR9 stimulated by HSV triggers the production of IFN-α [83]. Furthermore, TLR7 also play a role implied in MS. TLR7 trigger the maturation and differentiation status of B cells into immunoglobulin (Ig)-secreting plasma cells leads to the releasing of IgM and IgG. It is indicated that deficient TLR7-induced Immunoglobulin production in MS recently. The MS aggravation could be associated with impaired immune responses against infections with TLR7-recognized RNA viruses [84, 85].

The SNP rs243324 of SOCS1 variant regarded as risk factor for MS in a separate cohort of 3919 MS patients and 4003 controls in Spain population. Moreover, its T allele was increased in relapsing remitting (RR) MS which also named secondary-progressive MS patients than primary-progressive MS patients [86].

SOCS proteins, especially SOCS1 and SOCS3, not only expressed in immune cells but also have been described in the cells of the central nervous system (CNS). Besides the immunomodulating functions in the immune system, SOCS family also activate microglia, macrophages and astrocytes [87]. A moderated negative correlation has been depicted between SOCS1 and SOCS3. SOCS1 transcription level was lower in the peripheral blood leukocytes of MS patients compared with healthy controls, while SOCS3 was shown to have higher transcription level [88]. The presence of SOCS1 inhibit the process of IFN-γ induction of TNF-α secretion and STAT-1α and NF-κB activation, results in the reduction of CD40 both at protein and mRNA levels [89].

The expression level of SOCS3 is lower in $CD4^+$ and $CD8^+$ T cells from RR MS patients during relapse compared with MS patients in remission [90]. Lower expression level of SOCS3 results in increasing the activation of STAT3, causing massive release of the hormone leptin in CSF of MS patients and

other MS lesions [91]. Leptin has the function of triggering TNF-α, IL-6 and IL-10 expression in monocytes of relapsing MS patients but not in monocytes of the patients with stable disease stage. Indeed, decreased SOCS3 expression level during relapses might account for overexpression of leptin-mediated cytokine in MS [92]. On the other hand, Th17 cells have been implied to have an essential role in pathomechanism of autoimmune diseases. Th17 cell lineage transcription factors, signal transducer and activator of the transcription (i.e. STAT 3) lead to the activation of the specific cytokines close associated with Th17, including IL-17A, IL-17F, IL-21 and IL-22. It is indicated that IL-1 receptor type 1 (IL-1R1) signaling is highly related with the differentiation and activation of Th17 cells. IL-1R1 signaling induces Th17 cell differentiation results in the expression of IRAK4 together with retinoic acid-related orphan nuclear hormone receptor (ROR). Therapeutic strategies with inhibiting IL-1R1 signaling can be regarded as a novel approach for the treatment of MS based on the role of IL-1 signaling and Th17 cells in the development of the autoimmune processes and autoimmune diseases. Negative regulators including inhibitory membrane-bound IL-RII, the regulatory IL-1R1 antagonist (IL-1R1a) and the IL-1R1-signlaing-induced single Ig IL-1R-related (SIGIRR) suppress excessive IL-1 signaling and Th17 cell differentiation [93]. IFN-β has been used as preferred therapy for MS by suppressing the differentiation of Th17 cells via inducing the production of Th17-suppressive cytokines including IL-27 and IL-12 in DCs. SOCS3 regarded as important regulator of leptin-mediated protein, inhibited the production of the Th17-promoting cytokines IL-6 and IL-23 [94]. Surprisingly, statins used for controlling cholesterol levels such as simvastatin also have anti-inflammatory and immunomodulatory effects. It induces SOCS3 expression in monocytes from RR MS patients leads to the lower activation of STAT1 and STAT3, which blocks the development of Th17 cells. The production of Th17-promoting cytokines IL-6 and IL-23 is further inhibited as the

result, leading to the decreased IL-17 production and inhibition of the expression of IL-17 transcription factor RORC in $CD4^+$ T cells [95, 96]. Statins blocks the development of Th17 might be protective in MS, therefore, they are being tested in clinical trials in MS patients currently [97].

Additionally, torque teno virus (TTV) also involed in the pathogenesis of MS. TTV interact with TLRs, which leads to the production of inflammatory cytokines, contributing to the chronic disease progression in MS patients. Overexpression of TLR9 on monocytes of MS patients is correlated with higher titers of TTV in blood [98].

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a common autoimmune disorder with prevalence rates approximately 1% of the adults worldwide. The disease primarily affects the synovial joints and the chronic inflammatory process consequently causes the destruction of the articular tissue [99].

Several genetic studies address the association of the common SNP of TLR and the pathogenesis of RA. The results somewhat vary from region to region. The TLR9 SNP rs187084 allele variant TT may increase RA susceptibility in the Turkish RA population, although it was not associated in studies of Dutch or French cohorts [100–102]. Furthermore, the SNP rs5741883 of TLR8 has been reavealed to have association with rheumatoid factor autoantibody positivity in a cohort study on 319 European individuals [103].

Besides the assessment of SNP of TLRs in RA patients, functional studies on TLRs in human RA samples identified increased activation status of these receptors. It is suggested that the adaptor protein used by most TLRs, MyD88, is essential in matrix metalloproteinase (MMP) production which is responsible for the tissue destruction and remodeling in RA synovial membrane cultures [104]. Therefore, TLRs have potential involvement in the inflammatory and destructive processes in RA. Furthermore, TLR3 can also promote

osteoclasto-genesis via up-regulation of receptor activator of nuclear factor κB ligand (RANKL, also known as osteoclast differentiation factor) on RA synovial fluids (SFs) causing chronic inflammation [105]. RA necrotic synovial fluid cells have been shown to release RNA regard as endogenous TLR3 ligand that can activate TLR3 on RASFs [106].

TLR signaling pathways have correlated with the development and maintenance of RA. Many studies have investigated the expression and function of TLRs in synovial tissue cells from patients compared with tissue samples from osteoarthritis (OA) patients or healthy controls. All endosomal TLRs included TLR3, TLR7, TLR8 and TLR9 expressed not only in peripheral blood but also in human synovial tissue of RA patients [106–108]. A variety of TLRs including TLR2, TLR3, TLR5, TLR6, TLR7 and TLR9 shown overexpression in the synovium of RA patients compared with healthy controls or OA patients [109–111]. TLR2 has essential pathogenic function in RA, activation of synovial fibroblasts via TLR2 induces the production of multiple inflammatory chemokines including IL-1β and TNF-α in RA joints [112, 113]. TLR2 and TLR4 expression was found associated with the presence of IL-12 and IL-18 in RA synovial tissue [111]. Activation of TLR-3 and TLR-7/8 resulted in a skewed balance toward IL-12 [114]. DCs derived from RA patients have shown elevated levels of inflammatory cytokines such as TNF-α and IL-6 mediated by activation of TLR2 and TLR4 compared with healthy controls [114]. Stimulation of synovial fibroblasts with the TLR3 ligand results in releasing IL-6, MMP-3 and MMP-13 [108]. It is observed that TLR8 induced the massive secretion of TNF from RA synovium. By using imiquimod (inhibition of spontaneous TNF production) specifically inhibit TLR8 [107].

Further data on the contribution of these TLRs in the perpetuation of inflammation in RA comes from studies with antimalarial drugs, such as chloroquine, hydroxychloroquine, and quinacrine, which have been

used to treat RA in the last century [115, 116]. These drugs act as antagonists of TLR9 and inhibit endosomal acidification [117]. They could also interact directly with nucleic acids, causing modifications which prevent their binding to the endosomal TLRs [118].

SOCS protein levels can dramatically modulate cellular responses to cytokines through the JAK-STAT pathway. The overexpression of SOCS1 and SOCS3 were detected in PBMCs from RA patients compared with healthy controls could relate with the up-regulation of SOCS1 in T cells and SOCS3 in monocytes. SOCS1 also had higher expression in the synovial membranes from RA patients compared with OA patients. Moreover, SOCS2 was up-regulated in T cells. Intriguingly, T cells in synovial fluid expressed lower levels of SOCS molecules than in the peripheral blood. Furthermore, macrophages in synovial fluid have higher levels of SOCS molecules than in the peripheral blood. [119] The transcript levels of CIS, SOCS1, SOCS2 and SOCS3 genes in RA patients compared with normal individuals were not reaching statistical significant level. However, the RA patients group using treatment with TNF-α blocking agent appeared to have over-expression level of CIS, but lower-expression of SOCS2 in PBMCs [67].

The expression of TNF-α and related signaling molecules were detected in PBMCs from 27 Indian RA samples and 30 controls. Significant overexpression of TNF-α and TNFR-I together with increased expression of TRADD, RIP, and TRAF2 mRNA indicated the enhanced signaling through TNFR-I-TRADD-RIP-TRAF2 pathway in RA patients compared with controls. Lower expression of FADD may suggest the suppressed signaling via TNFR-I-TRADD-FADD pathway [120].

Even though the role of variations in the TNF-α gene remains not completely known for the pathomechanism of RA, the factors regulating TNF-α signaling may contribute to RA susceptibility. The TRAF family members are one of the most characterised molecules transducing cytokine signals

from their cell surface receptors and activating downstream intracellular signaling cascades. The SNP rs7514863 of the TRAF5 gene identified a significant association across the entire cohort of 1273 cases with RA compared with 2463 healthy controls of UK Caucasian population [121].

Lee A et al. studied the TNF-α driven inflammatory program in fibroblast-like synoviocytes (FLSs) obtained from the synovial tissues of patients with RA. They discovered the TNF-α induced prolonged activation of NF-κB signaling and sustained transcriptional activity in FLSs of RA compared with OA. Moreover, lower expression of the feedback inhibitors A20-binding inhibitor of NF-κB activation 3 (ABIN3), IRAK-M, SOCS3 and activating transcription factor 3 (ATF3) was indicated in FLSs. Since those four factors may terminate inflammatory responses in macrophages, while in FLSs they had lower expression, resulting in uncontrolled inflammatory response which leads to persistent synovial inflammation in RA [122].

Systemic sclerosis

Systemic sclerosis (SSc) characterized by sclerosis in multiple systems including skin, lungs, the gastrointestinal tract, kidneys and the musculoskeletal system. SSc is classified into two sub-groups based on the extent of skin thickening: limited SSc and diffuse SSc. The limited form is at lower risk of visceral involvement, while the diffuse form involves several systems of internal organs. [123]

It is believed that many TLRs participate in the development of the dysfunction of the immune system in SSc. For instance, TLR agonist S100A8/A9 regarded as a novel possible marker for SSc phenotype [124]. A SNP of TLR2 (Pro631His) variant was suggested to be associated with the diffuse form of SSc and the development of pulmonary arterial hypertension (PAH) [125].

On the other hand, Siglec-1(CD169, sialoadhesin) is a IFN-regulated gene that was regarded as macrophage marker. Certain TLR agonists, including TLR-7 and TLR-9, trigger the induction of Siglec-1 mRNA and surface protein expression in circulating monocytes and tissue macrophages of SSc patients compared with healthy controls. By immunohistochemistry, they observed higher amounts of Siglec-1+ cells in the skin of SSc patients compared with controls. Up-regulated certain TLRs through the IFN-mediated gene imply their essential role in the pathomechanism of SSc [126].

The T-cell attracting and profibrotic chemokine CCL18 shown higher levels in SSc. The monocyte-derived DCs matured with the TLR4 ligand LPS from SSc patients release significantly increased levels of IL-10 compared with healthy controls, which suggest a role for TLR4 ligands in the pathogenesis of SSc [127].

Other profibrotic and proangiogenic chemokines such as CCL2 and CXCL8 have also shown relation with SSc. CCL2 production was sensitive to both inhibition of proteasome and JNK, while CXCL8 production was sensitive only to inhibition of proteasome. Excessive production of these two chemokines in antifibroblast antibodies (AFAs)-stimulated fibroblast culture supernatants resulted in activation of ERK-1/2, c-Jun, and NF-κB. Furthermore, anti-human TLR4 monoclonal antibodies (mAb) partially inhibited the production of CCL2 induced by AFAs in human fibroblasts, in other words, CCL2 induction is TLR4 dependent [128].

Autoantibodies that bind to the surface of fibroblasts may contribute to the pathogenesis of SSc. Furthermore, EBV activates TLR pathway in infected SSc fibroblasts. In EBV/p2089-infected SSc fibroblasts (*in vitro*), a significant induction of mRNA expression levels of TLR7 and TLR9, selected IFN-stimulated genes (ISGs), IRF7, IRF5, and IRF4 have been described [129].

MMPs are capable of degrading all extracellular matrix (ECM) components [130]. Tissue inhibitors of metalloproteinase (TIMPs) are induced by MyD88-dependent TLRs, especially TLR8, selectively inhibits MMPs to block the breakdown of ECM [130, 131]. TIMP-1 is the most characterized enzyme among the TIMP family since it can inhibit most MMPs [130]. Therefore higher serum concentrations of TIMP-1 result in the increment in the ratio of TIMP/MMP of patients with SSc [132–135]. Increased TIMP-1 production has been described in circulating monocytes of SSc compared with RA patients and controls. When SSc and control monocytes were stimulated with TLR8 agonist, TIMP-1 production dramatically elevated, underlining the role of TLR signaling in ECM remodeling [136].

Psoriasis

Psoriasis is a chronic and frequently relapsing inflammatory skin disease characterized by pathologic features such as accelerated epidermopoiesis, marked hyperkeratosis with parakeratosis (abnormal maturation), vascular dilatation, and inflammatory cell infiltration. The most common form of the disorder is the chronic plaque psoriasis with rounded erythematous, dry, scaling patches. The lesions have a predilection site as nails, scalp, genitalia, extensor surfaces, and the lumbosacral region. The etiology of the disease is not fully understood, but genetical factors are highly believed to be involved [137].

TLR1, TLR2, and TLR5 have been detected constitutively expressed on the normal keratinocytes in the epidermis. Interestingly, the expression of TLR1 and TLR2 on keratinocytes in the psoriasis skin lesions is further upregulated [138]. The higher expression of TLR4 in guttate psoriasis was indicated compared with plaque psoriasis and normal controls [139]. The enhanced TLR2 expression could further upregulate TLR4 expression in epidermal and dermal DCs of psoriatic skin [140]. Psoriatic

keratinocytes induce high levels of inflammatory mediators and become hyperproliferative upon IFN-γ and TNF-α stimuli, resulting in thickening of the skin. The TLR-7/8 agonist imiquimod stimulated IFN-γ and enhanced DCs infiltration, resulted in psoriatic exacerbations [141]. Among the other TLRs, TLR5 and TLR9 were upregulated by transforming growth factor-α (TGF-α) in psoriatic epidermal keratinocytes [142].

The common coding variants of TRAF3IP2 gene p.Asp10Asn allele (rs33980500) regarded as risk factor for psoriatic arthritis. Down-regulated TRAF3IP2 variant disrupted the binding property to TRAF6, indicating altered modulation of immunoregulatory signaling such as IL-17 in a German population [143, 144].

IFN-α and skin infiltrating activated T lymphocytes are also involved in the pathogenesis of psoriasis. Down-regulation of the SOCS3 together with SH2-domain-containing protein-tyrosine phosphatase 1(SHP1) in response to IFN-α was found in the psoriatic T cells compared to that of healthy controls [145]. Intriguingly, SOCS1, SOCS2, and SOCS3 proteins were barely undetectable and only weakly expressed in atopic dermatitis skin [146]. MiR-203 is the keratinocyte-derived microRNA with a highly skin-specific expression profile. Its up-regulation in psoriatic plaques was concurrent with down-regulation of SOCS3, which is a miR-203 conserved target [147].

Conversely, Federici M et al. found exaggerated expression of SOCS1 and SOCS3 in the psoriatic epidermis and allergic contact dermatitis in the IFN-γ and TNFα-activated psoriatic keratinocytes. By sustaining the activation of the PI3K/AKT pathway in keratinocytes, SOCS1 and SOCS3 could suppress cytokine-induced apoptosis by blocking the proteasome [148]. SOCS1 mimetic peptide to control IFN-γ-mediated skin disorders is regarded as a new future perspective in psoriasis therapy [149].

The expression of TNF-α and IL-8 induced by the TLR2, TLR3 and TLR4 signaling pathways via NF-κB nuclear translocation in human psoriatic keratinocytes have been described previously [150]. Some immunosuppressive therapies, such as pimecrolimus and tacrolimus work in the way that suppress TLR2 signaling, which leads to down-regulated of TNF-α and IL-8 mRNA expression in human keratinocytes to control psoriatic inflammation [151]. Topical retinoids also works as TLR2 inhibitors [152]. While monomethylfumarate interferes with LPS signaling that inhibits NF-κB via TLR 4 in dendritic cells results in lower expression of IL-12p70 and IL-10 [153].

Tables 3 summarized the association between SNPs and autoimmune diseases, while Table 4 summarized the association between TLRs and autoimmune diseases.

Future prospects

Activation of TLRs plays an important role in cytokine production in autoimmune diseases. IRAK, TRAF and SOCS proteins are regarded as the main modulators of the TLR pathways. Addressing their gene expression profile together with SNP elucidation could be important to explain this aspect of the pathomechanism driving autoimmune diseases. Moreover, more targeted therapeutical potential could be utilized with more background knowledge on the TLRs family, such as statins use for the treatment in MS. Further studies on the identification of new families of other innate receptors (CLRs, NLRs and RLRs) and their signaling pathways will help to understand individual TLR responses in innate immunity and aid more precisely in pinpointing therapeutic targets in patients with autoimmune diseases.

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References

1. Amital H, Govoni M, Maya R, et al (2008) Role of infectious agents in systemic rheumatic diseases. Clin Exp Rheumatol 26:S27–32.

2. Liu Y, Yin H, Zhao M, Lu Q (2014) TLR2 and TLR4 in autoimmune diseases: a comprehensive review. Clin Rev Allergy Immunol 47:136–147. doi: 10.1007/s12016-013-8402-y

3. Thwaites R, Chamberlain G, Sacre S (2014) Emerging role of endosomal toll-like receptors in rheumatoid arthritis. Front Immunol 5:1. doi: 10.3389/fimmu.2014.00001

4. Akira S, Uematsu S, Takeuchi O (2006) Pathogen recognition and innate immunity. Cell 124:783–801. doi: 10.1016/j.cell.2006.02.015

5. Santegoets KCM, van Bon L, van den Berg WB, et al (2011) Toll-like receptors in rheumatic diseases: are we paying a high price for our defense against bugs? FEBS Lett 585:3660–3666. doi: 10.1016/j.febslet.2011.04.028

6. Mogensen TH, Paludan SR (2005) Reading the viral signature by Toll-like receptors and other pattern recognition receptors. J Mol Med Berl Ger 83:180–192. doi: 10.1007/s00109-004-0620-6

7. Akira S, Takeda K (2004) Toll-like receptor signalling. Nat Rev Immunol 4:499–511. doi: 10.1038/nri1391

8. Bowie A, O'Neill LA (2000) The interleukin-1 receptor/Toll-like receptor superfamily: signal generators for pro-inflammatory interleukins and microbial products. J Leukoc Biol 67:508–514.

9. Kawai T, Akira S (2011) Toll-like receptors and their crosstalk with other innate receptors in infection and immunity. Immunity 34:637–650. doi: 10.1016/j.immuni.2011.05.006

10. Roach JC, Glusman G, Rowen L, et al (2005) The evolution of vertebrate Toll-like receptors. Proc Natl Acad Sci U S A 102:9577–9582. doi: 10.1073/pnas.0502272102

11. Takeda K, Akira S (2005) Toll-like receptors in innate immunity. Int Immunol 17:1–14. doi: 10.1093/intimm/dxh186

12. Yamamoto M, Sato S, Mori K, et al (2002) Cutting edge: a novel Toll/IL-1 receptor domain-containing adapter that preferentially activates the IFN-beta promoter in the Toll-like receptor signaling. J Immunol Baltim Md 1950 169:6668–6672.

13. Yamamoto M, Sato S, Hemmi H, et al (2003) Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. Science 301:640–643. doi: 10.1126/science.1087262

14. Horng T, Barton GM, Flavell RA, Medzhitov R (2002) The adaptor molecule TIRAP provides signalling specificity for Toll-like receptors. Nature 420:329–333. doi: 10.1038/nature01180

15. Honda K, Yanai H, Mizutani T, et al (2004) Role of a transductional-transcriptional processor complex involving MyD88 and IRF-7 in Toll-like receptor signaling. Proc Natl Acad Sci U S A 101:15416–15421. doi: 10.1073/pnas.0406933101

16. Negishi H, Fujita Y, Yanai H, et al (2006) Evidence for licensing of IFN-gamma-induced IFN regulatory factor 1 transcription factor by MyD88 in Toll-like receptor-dependent gene induction program. Proc Natl Acad Sci U S A 103:15136–15141. doi: 10.1073/pnas.0607181103

17. Takaoka A, Yanai H, Kondo S, et al (2005) Integral role of IRF-5 in the gene induction programme activated by Toll-like receptors. Nature 434:243–249. doi: 10.1038/nature03308

18. Kagan JC, Su T, Horng T, et al (2008) TRAM couples endocytosis of Toll-like receptor 4 to the induction of interferon-beta. Nat Immunol 9:361–368. doi: 10.1038/ni1569

19. Kawai T, Akira S (2010) The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol 11:373–384. doi: 10.1038/ni.1863

20. Shimazu R, Akashi S, Ogata H, et al (1999) MD-2, a molecule that confers lipopolysaccharide responsiveness on Toll-like receptor 4. J Exp Med 189:1777–1782.

21. Kurt-Jones EA, Popova L, Kwinn L, et al (2000) Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus. Nat Immunol 1:398–401. doi: 10.1038/80833

22. Cao Z, Henzel WJ, Gao X (1996) IRAK: a kinase associated with the interleukin-1 receptor. Science 271:1128–1131.

23. Janssens S, Beyaert R (2003) Functional diversity and regulation of different interleukin-1 receptor-associated kinase (IRAK) family members. Mol Cell 11:293–302.

24. O'Neill LAJ, Bryant CE, Doyle SL (2009) Therapeutic targeting of Toll-like receptors for infectious and inflammatory diseases and cancer. Pharmacol Rev 61:177–197. doi: 10.1124/pr.109.001073

25. Wang C, Deng L, Hong M, et al (2001) TAK1 is a ubiquitin-dependent kinase of MKK and IKK. Nature 412:346–351. doi: 10.1038/35085597

26. Hsu H, Xiong J, Goeddel DV (1995) The TNF receptor 1-associated protein TRADD signals cell death and NF-kappa B activation. Cell 81:495–504.

27. Youn J, Kim H-Y, Park JH, et al (2002) Regulation of TNF-alpha-mediated hyperplasia through TNF receptors, TRAFs, and NF-kappaB in synoviocytes obtained from patients with rheumatoid arthritis. Immunol Lett 83:85–93.

28. Rothe M, Sarma V, Dixit VM, Goeddel DV (1995) TRAF2-mediated activation of NF-kappa B by TNF receptor 2 and CD40. Science 269:1424–1427.

29. Ihnatko R, Kubes M (2007) TNF signaling: early events and phosphorylation. Gen Physiol Biophys 26:159–167.

30. Chung JY, Lu M, Yin Q, et al (2007) Molecular basis for the unique specificity of TRAF6. Adv Exp Med Biol 597:122–130. doi: 10.1007/978-0-387-70630-6_10

31. Lee NK, Lee SY (2002) Modulation of life and death by the tumor necrosis factor receptor-associated factors (TRAFs). J Biochem Mol Biol 35:61–66.

32. Bradley JR, Pober JS (2001) Tumor necrosis factor receptor-associated factors (TRAFs). Oncogene 20:6482–6491. doi: 10.1038/sj.onc.1204788

33. Wu H, Arron JR (2003) TRAF6, a molecular bridge spanning adaptive immunity, innate immunity and osteoimmunology. BioEssays News Rev Mol Cell Dev Biol 25:1096–1105. doi: 10.1002/bies.10352

34. Naito A, Azuma S, Tanaka S, et al (1999) Severe osteopetrosis, defective interleukin-1 signalling and lymph node organogenesis in TRAF6-deficient mice. Genes Cells Devoted Mol Cell Mech 4:353–362.

35. Endo TA, Masuhara M, Yokouchi M, et al (1997) A new protein containing an SH2 domain that inhibits JAK kinases. Nature 387:921–924. doi: 10.1038/43213

36. Starr R, Willson TA, Viney EM, et al (1997) A family of cytokine-inducible inhibitors of signalling. Nature 387:917–921. doi: 10.1038/43206

37. Naka T, Narazaki M, Hirata M, et al (1997) Structure and function of a new STAT-induced STAT inhibitor. Nature 387:924–929. doi: 10.1038/43219

38. Li YC, Chen Y, Liu W, Thadhani R (2014) MicroRNA-mediated mechanism of vitamin D regulation of innate immune response. J Steroid Biochem Mol Biol 144 Pt A:81–86. doi: 10.1016/j.jsbmb.2013.09.014

39. Mansell A, Smith R, Doyle SL, et al (2006) Suppressor of cytokine signaling 1 negatively regulates Toll-like receptor signaling by mediating Mal degradation. Nat Immunol 7:148–155. doi: 10.1038/ni1299

40. Zeher M, Szodoray P (2009) Sjögren's syndrome and associated disorders. Transworld Research Network, Kerala, India

41. Szanto A, Szodoray P, Kiss E, et al (2006) Clinical, serologic, and genetic profiles of patients with associated Sjögren's syndrome and systemic lupus erythematosus. Hum Immunol 67:924–930. doi: 10.1016/j.humimm.2006.06.006

42. Zheng L, Zhang Z, Yu C, Yang C (2010) Expression of Toll-like receptors 7, 8, and 9 in primary Sjögren's syndrome. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 109:844–850. doi: 10.1016/j.tripleo.2010.01.006

43. Spachidou MP, Bourazopoulou E, Maratheftis CI, et al (2007) Expression of functional Toll-like receptors by salivary gland epithelial cells: increased mRNA expression in cells derived from patients with primary Sjögren's syndrome. Clin Exp Immunol 147:497–503. doi: 10.1111/j.1365-2249.2006.03311.x

44. Kawakami A, Nakashima K, Tamai M, et al (2007) Toll-like receptor in salivary glands from patients with Sjögren's syndrome: functional analysis by human salivary gland cell line. J Rheumatol 34:1019–1026.

45. Kwok S-K, Cho M-L, Her Y-M, et al (2012) TLR2 ligation induces the production of IL-23/IL-17 via IL-6, STAT3 and NF-kB pathway in patients with primary Sjogren's syndrome. Arthritis Res Ther 14:R64. doi: 10.1186/ar3780

46. Zilahi E, Tarr T, Papp G, et al (2012) Increased microRNA-146a/b, TRAF6 gene and decreased IRAK1 gene expressions in the peripheral mononuclear cells of patients with Sjögren's syndrome. Immunol Lett 141:165–168. doi: 10.1016/j.imlet.2011.09.006

47. Bhaumik D, Scott GK, Schokrpur S, et al (2008) Expression of microRNA-146 suppresses NF-kappaB activity with reduction of metastatic potential in breast cancer cells. Oncogene 27:5643–5647. doi: 10.1038/onc.2008.171

48. Szodoray P, Gal I, Barath S, et al (2008) Immunological alterations in newly diagnosed primary Sjögren's syndrome characterized by skewed peripheral T-cell subsets and inflammatory cytokines. Scand J Rheumatol 37:205–212. doi: 10.1080/03009740801910361

49. Rothfield N (1989) Clinical aspects and treatment of systemic lupus erythematosus. Curr Opin Rheumatol 1:327–331.

50. Savarese E, Chae O, Trowitzsch S, et al (2006) U1 small nuclear ribonucleoprotein immune complexes induce type I interferon in plasmacytoid dendritic cells through TLR7. Blood 107:3229–3234. doi: 10.1182/blood-2005-07-2650

51. Vollmer J, Tluk S, Schmitz C, et al (2005) Immune stimulation mediated by autoantigen binding sites within small nuclear RNAs involves Toll-like receptors 7 and 8. J Exp Med 202:1575–1585. doi: 10.1084/jem.20051696

52. Means TK, Latz E, Hayashi F, et al (2005) Human lupus autoantibody-DNA complexes activate DCs through cooperation of CD32 and TLR9. J Clin Invest 115:407–417. doi: 10.1172/JCI23025

53. Barrat FJ, Meeker T, Gregorio J, et al (2005) Nucleic acids of mammalian origin can act as endogenous ligands for Toll-like receptors and may promote systemic lupus erythematosus. J Exp Med 202:1131–1139. doi: 10.1084/jem.20050914

54. Bengtsson AA, Sturfelt G, Truedsson L, et al (2000) Activation of type I interferon system in systemic lupus erythematosus correlates with disease activity but not with antiretroviral antibodies. Lupus 9:664–671.

55. Baechler EC, Batliwalla FM, Karypis G, et al (2003) Interferon-inducible gene expression signature in peripheral blood cells of patients with severe lupus. Proc Natl Acad Sci U S A 100:2610–2615. doi: 10.1073/pnas.0337679100

56. Honda K, Ohba Y, Yanai H, et al (2005) Spatiotemporal regulation of MyD88-IRF-7 signalling for robust type-I interferon induction. Nature 434:1035–1040. doi: 10.1038/nature03547

57. Napolitani G, Rinaldi A, Bertoni F, et al (2005) Selected Toll-like receptor agonist combinations synergistically trigger a T helper type 1-polarizing program in dendritic cells. Nat Immunol 6:769–776. doi: 10.1038/ni1223

58. Dennehy KM, Willment JA, Williams DL, Brown GD (2009) Reciprocal regulation of IL-23 and IL-12 following co-activation of Dectin-1 and TLR signaling pathways. Eur J Immunol 39:1379–1386. doi: 10.1002/eji.200838543

59. Lyn-Cook BD, Xie C, Oates J, et al (2014) Increased expression of Toll-like receptors (TLRs) 7 and 9 and other cytokines in systemic lupus erythematosus (SLE) patients: ethnic differences and potential new targets for therapeutic drugs. Mol Immunol 61:38–43. doi: 10.1016/j.molimm.2014.05.001

60. Castiblanco J, Varela D-C, Castaño-Rodríguez N, et al (2008) TIRAP (MAL) S180L polymorphism is a common protective factor against developing tuberculosis and systemic lupus erythematosus. Infect Genet Evol J Mol Epidemiol Evol Genet Infect Dis 8:541–544. doi: 10.1016/j.meegid.2008.03.001

61. Zhang J, Zhu Q, Meng F, et al (2014) Association study of TLR-9 polymorphisms and systemic lupus erythematosus in northern Chinese Han population. Gene 533:385–388. doi: 10.1016/j.gene.2013.08.051

62. Wang C-M, Chang S-W, Wu Y-JJ, et al (2014) Genetic variations in Toll-like receptors (TLRs 3/7/8) are associated with systemic lupus erythematosus in a Taiwanese population. Sci Rep 4:3792. doi: 10.1038/srep03792

63. Zhou X-J, Lv J-C, Cheng W-R, et al (2010) Association of TLR9 gene polymorphisms with lupus nephritis in a Chinese Han population. Clin Exp Rheumatol 28:397–400.

64. Laska MJ, Troldborg A, Hansen B, et al (2014) Polymorphisms within Toll-like receptors are associated with systemic lupus erythematosus in a cohort of Danish females. Rheumatol Oxf Engl 53:48–55. doi: 10.1093/rheumatology/ket316

65. Sánchez E, García-Bermúdez M, Jiménez-Alonso J, et al (2012) Association study of IRAK-M and SIGIRR genes with SLE in a large European-descent population. Lupus 21:1166–1171. doi: 10.1177/0961203312449494

66. Zhu L, Yang X, Chen W, et al (2007) Decreased expressions of the TNF-alpha signaling adapters in peripheral blood mononuclear cells (PBMCs) are correlated with disease activity in patients with systemic lupus erythematosus. Clin Rheumatol 26:1481–1489. doi: 10.1007/s10067-006-0531-8

67. Tsao J-T, Kuo C-C, Lin S-C (2008) The analysis of CIS, SOCS1, SOSC2 and SOCS3 transcript levels in peripheral blood mononuclear cells of systemic lupus erythematosus and rheumatoid arthritis patients. Clin Exp Med 8:179–185. doi: 10.1007/s10238-008-0006-0

68. Li J, Zhao S, Yi M, et al (2011) Activation of JAK-STAT1 signal transduction pathway in lesional skin and monocytes from patients with systemic lupus erythematosus. Zhong Nan Da Xue Xue Bao Yi Xue Ban 36:109–115. doi: 10.3969/j.issn.1672-7347.2011.02.003

69. Pierangeli SS, Vega‐Ostertag ME, Raschi E, et al (2007) Toll‐like receptor and antiphospholipid mediated thrombosis: in vivo studies. Ann Rheum Dis 66:1327–1333. doi: 10.1136/ard.2006.065037

70. Polman CH, Reingold SC, Edan G, et al (2005) Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria." Ann Neurol 58:840–846. doi: 10.1002/ana.20703

71. Gveric D, Kaltschmidt C, Cuzner ML, Newcombe J (1998) Transcription factor NF-kappaB and inhibitor I kappaBalpha are localized in macrophages in active multiple sclerosis lesions. J Neuropathol Exp Neurol 57:168–178.

72. Christophi GP, Panos M, Hudson CA, et al (2009) Macrophages of multiple sclerosis patients display deficient SHP-1 expression and enhanced inflammatory phenotype. Lab Investig J Tech Methods Pathol 89:742–759. doi: 10.1038/labinvest.2009.32

73. Reynolds JM, Martinez GJ, Chung Y, Dong C (2012) Toll-like receptor 4 signaling in T cells promotes autoimmune inflammation. Proc Natl Acad Sci U S A 109:13064–13069. doi: 10.1073/pnas.1120585109

74. Rolls A, Shechter R, London A, et al (2007) Toll-like receptors modulate adult hippocampal neurogenesis. Nat Cell Biol 9:1081–1088. doi: 10.1038/ncb1629

75. Kostjuk S, Loseva P, Chvartatskaya O, et al (2012) Extracellular GC-rich DNA activates TLR9- and NF-kB-dependent signaling pathways in human adipose-derived mesenchymal stem cells (haMSCs). Expert Opin Biol Ther 12 Suppl 1:S99–111. doi: 10.1517/14712598.2012.690028

76. Sloane JA, Batt C, Ma Y, et al (2010) Hyaluronan blocks oligodendrocyte progenitor maturation and remyelination through TLR2. Proc Natl Acad Sci U S A 107:11555–11560. doi: 10.1073/pnas.1006496107

77. Hanafy KA, Sloane JA (2011) Regulation of remyelination in multiple sclerosis. FEBS Lett 585:3821–3828. doi: 10.1016/j.febslet.2011.03.048

78. Hirotani M, Niino M, Fukazawa T, et al (2010) Decreased IL-10 production mediated by Toll-like receptor 9 in B cells in multiple sclerosis. J Neuroimmunol 221:95–100. doi: 10.1016/j.jneuroim.2010.02.012

79. Liu Y-J (2005) IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. Annu Rev Immunol 23:275–306. doi: 10.1146/annurev.immunol.23.021704.115633

80. Compton T, Kurt-Jones EA, Boehme KW, et al (2003) Human cytomegalovirus activates inflammatory cytokine responses via CD14 and Toll-like receptor 2. J Virol 77:4588–4596.

81. Dolganiuc A, Oak S, Kodys K, et al (2004) Hepatitis C core and nonstructural 3 proteins trigger toll-like receptor 2-mediated pathways and inflammatory activation. Gastroenterology 127:1513–1524.

82. Bieback K, Lien E, Klagge IM, et al (2002) Hemagglutinin protein of wild-type measles virus activates toll-like receptor 2 signaling. J Virol 76:8729–8736.

83. Rizzo R, Gentili V, Casetta I, et al (2012) Altered natural killer cells' response to herpes virus infection in multiple sclerosis involves KIR2DL2 expression. J Neuroimmunol 251:55–64. doi: 10.1016/j.jneuroim.2012.07.004

84. Hernández-Pedro NY, Espinosa-Ramirez G, de la Cruz VP, et al (2013) Initial immunopathogenesis of multiple sclerosis: innate immune response. Clin Dev Immunol 2013:413465. doi: 10.1155/2013/413465

85. Giacomini E, Severa M, Rizzo F, et al (2013) IFN-β therapy modulates B-cell and monocyte crosstalk via TLR7 in multiple sclerosis patients. Eur J Immunol 43:1963–1972. doi: 10.1002/eji.201243212

86. Vandenbroeck K, Alvarez J, Swaminathan B, et al (2012) A cytokine gene screen uncovers SOCS1 as genetic risk factor for multiple sclerosis. Genes Immun 13:21–28. doi: 10.1038/gene.2011.44

87. Baker BJ, Akhtar LN, Benveniste EN (2009) SOCS1 and SOCS3 in the control of CNS immunity. Trends Immunol 30:392–400. doi: 10.1016/j.it.2009.07.001

88. Sedeño-Monge V, Arcega-Revilla R, Rojas-Morales E, et al (2014) Quantitative analysis of the suppressors of cytokine signaling 1 and 3 in peripheral blood leukocytes of patients with multiple sclerosis. J Neuroimmunol 273:117–119. doi: 10.1016/j.jneuroim.2014.05.013

89. Wesemann DR, Dong Y, O'Keefe GM, et al (2002) Suppressor of cytokine signaling 1 inhibits cytokine induction of CD40 expression in macrophages. J Immunol Baltim Md 1950 169:2354–2360.

90. Frisullo G, Mirabella M, Angelucci F, et al (2007) The effect of disease activity on leptin, leptin receptor and suppressor of cytokine signalling-3 expression in relapsing-remitting multiple sclerosis. J Neuroimmunol 192:174–183. doi: 10.1016/j.jneuroim.2007.08.008

91. Matarese G, Carrieri PB, La Cava A, et al (2005) Leptin increase in multiple sclerosis associates with reduced number of CD4(+)CD25+ regulatory T cells. Proc Natl Acad Sci U S A 102:5150–5155. doi: 10.1073/pnas.0408995102

92. Bjørbaek C, Elmquist JK, Frantz JD, et al (1998) Identification of SOCS-3 as a potential mediator of central leptin resistance. Mol Cell 1:619–625.

93. Sha Y, Markovic-Plese S (2011) A role of IL-1R1 signaling in the differentiation of Th17 cells and the development of autoimmune diseases. Self/Nonself 2:35–42. doi: 10.4161/self.2.1.15639

94. Ramgolam VS, Markovic-Plese S (2010) Interferon-beta inhibits Th17 cell differentiation in patients with multiple sclerosis. Endocr Metab Immune Disord Drug Targets 10:161–167.

95. Zhang X, Jin J, Peng X, et al (2008) Simvastatin inhibits IL-17 secretion by targeting multiple IL-17-regulatory cytokines and by inhibiting the expression of IL-17 transcription factor RORC in CD4+ lymphocytes. J Immunol Baltim Md 1950 180:6988–6996.

96. Chen Z, Laurence A, Kanno Y, et al (2006) Selective regulatory function of Socs3 in the formation of IL-17-secreting T cells. Proc Natl Acad Sci U S A 103:8137–8142. doi: 10.1073/pnas.0600666103

97. Weber MS, Zamvil SS (2008) Statins and demyelination. Curr Top Microbiol Immunol 318:313–324.

98. Mancuso R, Saresella M, Hernis A, et al (2013) Torque teno virus (TTV) in multiple sclerosis patients with different patterns of disease. J Med Virol 85:2176–2183. doi: 10.1002/jmv.23707

99. Gibofsky A (2012) Overview of epidemiology, pathophysiology, and diagnosis of rheumatoid arthritis. Am J Manag Care 18:S295–302.

100. Coenen MJH, Enevold C, Barrera P, et al (2010) Genetic variants in toll-like receptors are not associated with rheumatoid arthritis susceptibility or anti-tumour necrosis factor treatment outcome. PloS One 5:e14326. doi: 10.1371/journal.pone.0014326

101. Jaen O, Petit-Teixeira E, Kirsten H, et al (2009) No evidence of major effects in several Toll-like receptor gene polymorphisms in rheumatoid arthritis. Arthritis Res Ther 11:R5. doi: 10.1186/ar2589

102. Etem EO, Elyas H, Ozgocmen S, et al (2011) The investigation of toll-like receptor 3, 9 and 10 gene polymorphisms in Turkish rheumatoid arthritis patients. Rheumatol Int 31:1369–1374. doi: 10.1007/s00296-010-1472-8

103. Enevold C, Radstake TRD, Coenen MJH, et al (2010) Multiplex screening of 22 single-nucleotide polymorphisms in 7 Toll-like receptors: an association study in rheumatoid arthritis. J Rheumatol 37:905–910. doi: 10.3899/jrheum.090775

104. Sacre SM, Andreakos E, Kiriakidis S, et al (2007) The Toll-like receptor adaptor proteins MyD88 and Mal/TIRAP contribute to the inflammatory and destructive processes in a human model of rheumatoid arthritis. Am J Pathol 170:518–525. doi: 10.2353/ajpath.2007.060657

105. Kim K-W, Cho M-L, Oh H-J, et al (2009) TLR-3 enhances osteoclastogenesis through upregulation of RANKL expression from fibroblast-like synoviocytes in patients with rheumatoid arthritis. Immunol Lett 124:9–17. doi: 10.1016/j.imlet.2009.02.006

106. Brentano F, Schorr O, Gay RE, et al (2005) RNA released from necrotic synovial fluid cells activates rheumatoid arthritis synovial fibroblasts via Toll-like receptor 3. Arthritis Rheum 52:2656–2665. doi: 10.1002/art.21273

107. Sacre SM, Lo A, Gregory B, et al (2008) Inhibitors of TLR8 reduce TNF production from human rheumatoid synovial membrane cultures. J Immunol Baltim Md 1950 181:8002–8009.

108. Ospelt C, Brentano F, Rengel Y, et al (2008) Overexpression of toll-like receptors 3 and 4 in synovial tissue from patients with early rheumatoid arthritis: toll-like receptor expression in early and longstanding arthritis. Arthritis Rheum 58:3684–3692. doi: 10.1002/art.24140

109. Roelofs MF, Wenink MH, Brentano F, et al (2009) Type I interferons might form the link between Toll-like receptor (TLR) 3/7 and TLR4-mediated synovial inflammation in rheumatoid arthritis (RA). Ann Rheum Dis 68:1486–1493. doi: 10.1136/ard.2007.086421

110. Tamaki Y, Takakubo Y, Hirayama T, et al (2011) Expression of Toll-like receptors and their signaling pathways in rheumatoid synovitis. J Rheumatol 38:810–820. doi: 10.3899/jrheum.100732

111. Radstake TRDJ, Roelofs MF, Jenniskens YM, et al (2004) Expression of toll-like receptors 2 and 4 in rheumatoid synovial tissue and regulation by proinflammatory cytokines interleukin-12 and interleukin-18 via interferon-gamma. Arthritis Rheum 50:3856–3865. doi: 10.1002/art.20678

112. Seibl R, Birchler T, Loeliger S, et al (2003) Expression and regulation of Toll-like receptor 2 in rheumatoid arthritis synovium. Am J Pathol 162:1221–1227. doi: 10.1016/S0002-9440(10)63918-1

113. Pierer M, Rethage J, Seibl R, et al (2004) Chemokine secretion of rheumatoid arthritis synovial fibroblasts stimulated by Toll-like receptor 2 ligands. J Immunol Baltim Md 1950 172:1256–1265.

114. Roelofs MF, Joosten L a. B, Abdollahi-Roodsaz S, et al (2005) The expression of toll-like receptors 3 and 7 in rheumatoid arthritis synovium is increased and costimulation of toll-like receptors 3, 4, and 7/8 results in synergistic cytokine production by dendritic cells. Arthritis Rheum 52:2313–2322. doi: 10.1002/art.21278

115. Maksymowych W, Russell AS (1987) Antimalarials in rheumatology: efficacy and safety. Semin Arthritis Rheum 16:206–221.

116. Khraishi MM, Singh G (1996) The role of anti-malarials in rheumatoid arthritis--the American experience. Lupus 5 Suppl 1:S41–44.

117. Sanjuan MA, Rao N, Lai K-TA, et al (2006) CpG-induced tyrosine phosphorylation occurs via a TLR9-independent mechanism and is required for cytokine secretion. J Cell Biol 172:1057–1068. doi: 10.1083/jcb.200508058

118. Kuznik A, Bencina M, Svajger U, et al (2011) Mechanism of endosomal TLR inhibition by antimalarial drugs and imidazoquinolines. J Immunol Baltim Md 1950 186:4794–4804. doi: 10.4049/jimmunol.1000702

119. Isomäki P, Alanärä T, Isohanni P, et al (2007) The expression of SOCS is altered in rheumatoid arthritis. Rheumatol Oxf Engl 46:1538–1546. doi: 10.1093/rheumatology/kem198

120. Raghav SK, Gupta B, Agrawal C, et al (2006) Expression of TNF-alpha and related signaling molecules in the peripheral blood mononuclear cells of rheumatoid arthritis patients. Mediators Inflamm 2006:12682. doi: 10.1155/MI/2006/12682

121. Potter C, Eyre S, Cope A, et al (2007) Investigation of association between the TRAF family genes and RA susceptibility. Ann Rheum Dis 66:1322–1326. doi: 10.1136/ard.2006.065706

122. Lee A, Qiao Y, Grigoriev G, et al (2013) Tumor necrosis factor α induces sustained signaling and a prolonged and unremitting inflammatory response in rheumatoid arthritis synovial fibroblasts. Arthritis Rheum 65:928–938. doi: 10.1002/art.37853

123. Casale R, Buonocore M, Matucci-Cerinic M (1997) Systemic sclerosis (scleroderma): an integrated challenge in rehabilitation. Arch Phys Med Rehabil 78:767–773.

124. van Bon L, Cossu M, Loof A, et al (2014) Proteomic analysis of plasma identifies the Toll-like receptor agonists S100A8/A9 as a novel possible marker for systemic sclerosis phenotype. Ann Rheum Dis 73:1585–1589. doi: 10.1136/annrheumdis-2013-205013

125. Broen JCA, Bossini-Castillo L, van Bon L, et al (2012) A rare polymorphism in the gene for Toll-like receptor 2 is associated with systemic sclerosis phenotype and increases the production of inflammatory mediators. Arthritis Rheum 64:264–271. doi: 10.1002/art.33325

126. York MR, Nagai T, Mangini AJ, et al (2007) A macrophage marker, Siglec-1, is increased on circulating monocytes in patients with systemic sclerosis and induced by type I interferons and toll-like receptor agonists. Arthritis Rheum 56:1010–1020. doi: 10.1002/art.22382

127. van Lieshout AWT, Vonk MC, Bredie SJH, et al (2009) Enhanced interleukin-10 production by dendritic cells upon stimulation with Toll-like receptor 4 agonists in systemic sclerosis that is possibly implicated in CCL18 secretion. Scand J Rheumatol 38:282–290. doi: 10.1080/03009740802572467

128. Fineschi S, Goffin L, Rezzonico R, et al (2008) Antifibroblast antibodies in systemic sclerosis induce fibroblasts to produce profibrotic chemokines, with partial exploitation of toll-like receptor 4. Arthritis Rheum 58:3913–3923. doi: 10.1002/art.24049

129. Farina A, Cirone M, York M, et al (2014) Epstein-Barr virus infection induces aberrant TLR activation pathway and fibroblast-myofibroblast conversion in scleroderma. J Invest Dermatol 134:954–964. doi: 10.1038/jid.2013.423

130. Visse R, Nagase H (2003) Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res 92:827–839. doi: 10.1161/01.RES.0000070112.80711.3D

131. Woessner JF (1991) Matrix metalloproteinases and their inhibitors in connective tissue remodeling. FASEB J Off Publ Fed Am Soc Exp Biol 5:2145–2154.

132. Kikuchi K, Kubo M, Hoashi T, Tamaki K (2002) Decreased MMP-9 activity in the serum of patients with diffuse cutaneous systemic sclerosis. Clin Exp Dermatol 27:301–305.

133. Montagnana M, Volpe A, Lippi G, et al (2007) Relationship between matrix metalloproteinases/tissue inhibitors of matrix metalloproteinases systems and autoantibody patterns in systemic sclerosis. Clin Biochem 40:837–842. doi: 10.1016/j.clinbiochem.2007.03.023

134. Kikuchi K, Kubo M, Sato S, et al (1995) Serum tissue inhibitor of metalloproteinases in patients with systemic sclerosis. J Am Acad Dermatol 33:973–978.

135. Iredale JP, Benyon RC, Arthur MJ, et al (1996) Tissue inhibitor of metalloproteinase-1 messenger RNA expression is enhanced relative to interstitial collagenase messenger RNA in experimental liver injury and fibrosis. Hepatol Baltim Md 24:176–184. doi: 10.1002/hep.510240129

136. Ciechomska M, Huigens CA, Hügle T, et al (2013) Toll-like receptor-mediated, enhanced production of profibrotic TIMP-1 in monocytes from patients with systemic sclerosis: role of serum factors. Ann Rheum Dis 72:1382–1389. doi: 10.1136/annrheumdis-2012-201958

137. Christophers E (2001) Psoriasis--epidemiology and clinical spectrum. Clin Exp Dermatol 26:314–320.

138. Baker BS, Ovigne J-M, Powles AV, et al (2003) Normal keratinocytes express Toll-like receptors (TLRs) 1, 2 and 5: modulation of TLR expression in chronic plaque psoriasis. Br J Dermatol 148:670–679.

139. Seung NR, Park EJ, Kim CW, et al (2007) Comparison of expression of heat-shock protein 60, Toll-like receptors 2 and 4, and T-cell receptor gammadelta in plaque and guttate psoriasis. J Cutan Pathol 34:903–911. doi: 10.1111/j.1600-0560.2007.00756.x

140. Curry JL, Qin J-Z, Bonish B, et al (2003) Innate immune-related receptors in normal and psoriatic skin. Arch Pathol Lab Med 127:178–186. doi: 10.1043/0003-9985(2003)127<178:IIRRIN>2.0.CO;2

141. Gaspari AA (2006) Innate and adaptive immunity and the pathophysiology of psoriasis. J Am Acad Dermatol 54:S67–80. doi: 10.1016/j.jaad.2005.10.057

142. Miller LS, Sørensen OE, Liu PT, et al (2005) TGF-alpha regulates TLR expression and function on epidermal keratinocytes. J Immunol Baltim Md 1950 174:6137–6143.

143. Hüffmeier U, Uebe S, Ekici AB, et al (2010) Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. Nat Genet 42:996–999. doi: 10.1038/ng.688

144. Böhm B, Burkhardt H, Uebe S, et al (2012) Identification of low-frequency TRAF3IP2 coding variants in psoriatic arthritis patients and functional characterization. Arthritis Res Ther 14:R84. doi: 10.1186/ar3807

145. Eriksen KW, Woetmann A, Skov L, et al (2010) Deficient SOCS3 and SHP-1 expression in psoriatic T cells. J Invest Dermatol 130:1590–1597. doi: 10.1038/jid.2010.6

146. Madonna S, Scarponi C, Pallotta S, et al (2012) Anti-apoptotic effects of suppressor of cytokine signaling 3 and 1 in psoriasis. Cell Death Dis 3:e334. doi: 10.1038/cddis.2012.69

147. Sonkoly E, Wei T, Janson PCJ, et al (2007) MicroRNAs: novel regulators involved in the pathogenesis of psoriasis? PloS One 2:e610. doi: 10.1371/journal.pone.0000610

148. Federici M, Giustizieri ML, Scarponi C, et al (2002) Impaired IFN-gamma-dependent inflammatory responses in human keratinocytes overexpressing the suppressor of cytokine signaling 1. J Immunol Baltim Md 1950 169:434–442.

149. Kubo M (2013) Therapeutic hope for psoriasis offered by SOCS (suppressor of cytokine signaling) mimetic peptide. Eur J Immunol 43:1702–1705. doi: 10.1002/eji.201343748

150. Begon E, Michel L, Flageul B, et al (2007) Expression, subcellular localization and cytokinic modulation of Toll-like receptors (TLRs) in normal human keratinocytes: TLR2 up-regulation in psoriatic skin. Eur J Dermatol EJD 17:497–506. doi: 10.1684/ejd.2007.0264

151. Rappersberger K, Komar M, Ebelin M-E, et al (2002) Pimecrolimus identifies a common genomic anti-inflammatory profile, is clinically highly effective in psoriasis and is well tolerated. J Invest Dermatol 119:876–887. doi: 10.1046/j.1523-1747.2002.00694.x

152. Kang SSW, Kauls LS, Gaspari AA (2006) Toll-like receptors: applications to dermatologic disease. J Am Acad Dermatol 54:951–983; quiz 983–986. doi: 10.1016/j.jaad.2005.05.004

153. Litjens NHR, Rademaker M, Ravensbergen B, et al (2004) Monomethylfumarate affects polarization of monocyte-derived dendritic cells resulting in down-regulated Th1 lymphocyte responses. Eur J Immunol 34:565–575. doi: 10.1002/eji.200324174

Legends to figure

Fig. 1 Function and signalization of Toll-like receptors

Ten Toll-like receptors (TLRs) are grouped into extracellular (TLR1, TLR2, TLR4, TLR5, TLR6 and TLR10) and intracellular (TLR3, TLR7, TLR8 and TLR9) subtypes. TLR10 was indicated as originating from the TLR1/TLR6 precursor. TLR2 addressed as heterodimer in combination with TLR1 or TLR6. Different components of microbial cells could activate extracellular subtype TLRs, while TLR3, TLR7/TLR8 and TLR9 recognize viral double stranded RNA (dsRNA), single stranded RNA (ssRNA) and unmethylated CpG DNA, respectively.

Myeloid differentiation primary response 88 (MyD88) and TIR-domain-containing adaptor inducing interferon (IFN)-β (TRIF) are two main adaptor pathways in TLRs signaling transduction. These two adaptor pathways transmit the signal downstream and lead to induction of gene expression via transcription factors, such as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), activating protein (AP)-1 or interferon-response factor (IRF) 1, 3, 5 and 7. TLR3 is the only TLR that exclusively uses the TRIF-dependent pathways, whereas the other TLRs are restricted to the MyD88-dependent pathway. Exceptionally, TLR4 triggers both pathways by first activating the MyD88 pathway at the plasma membrane then the TRIF-pathway via TRIF-related adaptor molecule (TRAM) at the endosomes.

Fig. 2 Targeted proteins and pathways of Toll-like receptors

TLRs interact with Myeloid differentiation primary response 88 (MyD88) through MyD88-adaptor like (Mal). Activated IL-1 receptor associated kinase (IRAK) 4 could further phosphorylated IRAK1. Activated IRAK1 binds to TNF receptor associated factor (TRAF) 6 to form the IRAK1/TRAF6

complex, which activates TGF-β-activated kinase 1(TAK1) and their binding proteins (TAB1, TAB2 and TAB3) complex. Subsequently activates inhibitor of κB kinase (IKK) complex (IKK-α, IKK-β and NEMO/IKK-γ) and mitogen-activated protein kinase (MAPK) in different pathway, leads to activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activating protein (AP)-1. Furthermore, IRAK1 also imply a role in tumor necrosis factor receptor (TNFR) superfamily-induced signaling pathways. The TNFR separates into two groups based on whether the death domain presence or not. When TNFR-I interacts with the TNFR associated death domain (TRADD), it may lead to the recruitment of receptor interacting protein (RIP) and TRAF2 for NF-κB activation. The recruitment with Fas-associated death domain (FADD) result in programmed apoptosis. Even though the TNFR-II does not contain the death domain, the intracellular consensus motif could bind to TRAF2 directly.