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REVIEW

Innate immune response in systemic autoimmune diseases: a potential target of therapy

Alireza Hejrati[1] · Alireza Rafiei[2] · Mohsen Soltanshahi[2,3] · Shahnaz Hosseinzadeh[2,3] · Mina Dabiri[2,3] · Mahdi Taghadosi[4] · Saeid Taghiloo[2,3] · Davood Bashash[5] · Fatemeh Khorshidi[6] · Parisa Zafari[2,3]

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Abstract

Innate immunity refers to defense mechanisms that are always present, ready to combat microbes and other offending agents. Innate immunity acts as a first-line defense and activates the conventional immune responses; however, it has been speculated that the importance of innate immunity in initiation and development of some disorders is more than just the "first line of defense". Autoimmune diseases, caused by immune system overactivation, are among the most challenging scientific and clinical problems, and there is still much to be learned about their pathogenesis. We aimed to provide a comprehensive overview of available documents about the role of innate immunity in systemic autoimmune diseases including rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, polymyositis, and systemic sclerosis. This study highlights the innate immunity pathways or molecules that are under investigation for therapy of these diseases.

Keywords Autoimmunity · Innate immunity · Lupus · Polymyositis · Rheumatoid arthritis

Introduction

Immunity is a complicated concept that can be divided into two primary arms: the innate and adaptive systems. Innate immunity as the first-line defense against pathogens consists of physical barriers, soluble factors, and cells. Adaptive immunity is made up of a vast array of special cells called B and T lymphocytes (Frizinsky et al. 2019; Watts et al. 2017).

The breakdown of self-tolerance as the hallmark of autoimmunity is based on adaptive immunity, but innate immunity also has unique characteristics, which make it a central driver in some critical immune responses (Zouali and La Cava 2019). Autoimmunity is a consequence of the failure of self-tolerance and immune reaction against an autoantigen, which is classified as systemic or organ specific (Pozsgay et al. 2017). Systemic autoimmune diseases are a wide array of disorders including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren's syndrome, polymyositis (PM), and systemic sclerosis (Pasoto et al. 2019). This heterogeneous group of disorders is characterized by the presence of ubiquitously expressed autoantigens and the involvement of multiple tissues and organs (Fridkis-Hareli 2008). To the best of our knowledge, although the association between adaptive immunity and autoimmune disease has been extensively studied, the importance of innate immunity in the development of autoimmune disorders is yet to be determined. Considering the lack of cure for this kind of disease, which leads to the need for long-lasting treatment, studies on the basic research give us new insights to help identify novel therapeutic targets. This study highlights how innate immunity might affect systemic autoimmune diseases and presents therapies targeting innate immunity

✉ Parisa Zafari
pzafari.70@gmail.com; p.zafari@mazums.ac.ir

1 Department of Internal Medicine, Hazrat-E-Rasool General Hospital, Tehran, Iran

2 Department of Immunology, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

3 Student Research Committee, School of Medicine, Mazandaran University of Medical Sciences, Sari, Iran

4 Department of Immunology, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

5 Department of Hematology and Blood Banking, School of Allied Medical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

6 Department of Immunology, Faculty of Medical Sciences, Tarbiat Modares University, Tehran, Iran

components in systemic autoimmune diseases that are currently under investigation.

Rheumatoid arthritis

Rheumatoid arthritis is a systemic autoimmune disease that affects mainly joints, leading to chronic inflammation of joints, cartilage damage, bone erosion, and finally systemic complications (Croia et al. 2019). Although the etiology of RA has not been fully delineated, both innate and adaptive immune systems are indispensable in the pathogenesis of RA (Rana et al. 2018). In this review, we will focus on innate immune cells and their crucial roles in RA.

Macrophages (MQs) are significant immune cells and central players in the pathogenesis of RA. They are the main source of proinflammatory cytokines such as tumor necrosis factor (TNFα), interleukin-1 beta (IL-1β), and IL-6, which generate inflammatory responses and contribute to the destruction of cartilage and bone resorption in patients with RA (Udalova et al. 2016). Synovial MQ plays critical roles in the events driving inflammation, including immune cell recruitment, fibroblast cell expansion, and protease secretion, leading to synovium destruction (Kennedy et al. 2011). Researchers have indicated that the imbalance between M1 and M2 MQs has a critical role in the pathogenesis of RA (Wang et al. 2017). MQs in the synovial fluid of patients with RA produce large amounts of TNFα and IL-1β, important proinflammatory cytokines that are characteristically secreted by M1 MQ (Kennedy et al. 2011).

Neutrophils are the first immune cells that arrive at the inflammation site. Their function includes phagocytosis, production of reactive oxygen species (ROS), and generation of neutrophil extracellular traps (NETs) in host defense (Bach et al. 2020). NETs can be the key source of citrullinated autoantigens, which can trigger the progress of RA (Chen et al. 2018). Citrullinated autoantigens in NETs can be taken up by fibroblast-like synoviocytes (FLS), presented to T cells, and leading to expansion of T and B cell response in patients with RA (Carmona-Rivera et al. 2017). Proinflammatory cytokines such as TNFα, IL-6, IL-8, and IL-17A can increase NETs in RA neutrophils. Eventually, NETs stimulate more cytokine production and inflammation via activating FLS and MQs (Chen et al. 2018; Khandpur et al. 2013). Neutrophils in the synovial fluid of patients with RA produce B lymphocyte stimulator (BLyS) that contributes to the activation of autoreactive B lymphocytes (Assi et al. 2007); furthermore, synovial joint neutrophils produce receptor activator of nuclear factor kappa-B ligand (RANKL) that is implicated in the activation and differentiation of osteoclasts and bone erosion in patients with RA (O'Neil and Kaplan 2019). Immune complexes are the major activator of neutrophils in the RA joint, by interaction with the FCγ receptor on the neutrophils (Wright et al. 2014).

Dendritic cells (DCs), as dedicated professional antigen-presenting cells, are likely key players in the initiation of joint inflammation and implicated in RA development (Yu and Langridge 2017). There are an increased number of myeloid and plasmacytoid DCs (pDC) in the joints of patients with RA. Some studies have suggested that in the proinflammatory environment, such as synovial fluid of patients with RA, the function of DC is different. These cells have been proposed as an inflammatory DC subset (Lebre et al. 2008; Yu and Langridge 2017). Inflammatory DCs are the main inducer of IL-17-producing T helper (Th17) cells by the production of IL-23 in the RA synovium (Estrada-Capetillo et al. 2013; Yu and Langridge 2017). Smoking has some effects on DCs, such as modifying the antigens that DCs present and regulation of DC activity (Yu and Langridge 2017).

Natural killer (NK) cells play an important role in the pathogenesis of RA through the production of inflammatory cytokines and interaction with various immune cells in synovial tissue (Ahern and Brennan 2011). Some studies have indicated the increased NK cells in the synovium of patients with RA expressed elevated levels of activation markers and cytokines such as TNFα and interferon-γ (IFNγ) (Fogel et al. 2013). NK cells secrets IFNγ, which may involve in inflammation through induction of B cell activation, class switching, and DC maturation (Ahern and Brennan 2011).

FLS, non-immune cells in synovium, have a critical function in the pathogenesis of RA. In an inflammatory microenvironment, FLS produce chemokines such as CCL2, CCL5, CCL8, CXCL5, and CXCL10, which recruit monocytes and MQs, and subsequently contribute to the pathogenesis of RA and inflammation. Activated FLS produces high levels of RANKL, which is a significant factor for the differentiation of osteoclasts and bone resorption. FLS functions as an antigen-presenting cell and interacts with $CD4^+$ T cells; furthermore, FLS has critical roles in the differentiation of T cells with the production of cytokines (Yoshitomi 2019). FLS produces large amounts of B cell-activating factor (BAFF) and IL-6 that contribute to the maturation and survival of B cells (Hunter and Jones 2015; Yoshitomi 2019).

The significant function of mucosal surfaces in the pathogenesis of RA has been proved. There is some evidence that the first hit in breaking self-tolerance for RA may originate at the epithelial surfaces. Many risk factors such as smoking and periodontal disease, at oral and lung levels, involve autoimmunity by driving the production of citrullinated autoantigens, and consequently anti-citrullinated protein antibodies (ACPA) (Lucchino et al. 2019; Pentony et al. 2017). A strong association between ACPAs and the progress of RA has been confirmed in various phases of the disease in patients with RA (Kurowska et al. 2017). Gut dysbiosis contributes to the

inflammatory state through induced Th17 polarization and imbalance between Th17 and regulatory T cells (Lucchino et al. 2019).

Many studies show the pathologic role of mast cells (MC) in RA (Xu and Chen 2015). The number of MCs is increased in RA synovium. Activated MCs produce various mediators, cytokines, and chemokines that recruit inflammatory cells into synovium. The main source of IL-17A in RA synovium is MCs (Min et al. 2020). It is indicated that MCs enhance survival, activation, proliferation, and differentiation of naive B cells (Rivellese et al. 2018).

γδ T cells are mainly distributed in the mucosal and epithelial tissues. These cells have a significant role in autoimmune diseases such as RA. γδ T cells contribute to an escalated production of proinflammatory cytokines, pathogenic autoantibody, and finally lead to the initiation of this autoimmune disease (Sun 2013).

Various autoantibodies present in patients with RA, such as anti-collagen type II antibodies, ACPA, and rheumatoid factor that target antigens in cartilage and synovium, lead to the formation of immune complexes. These immune complexes can activate complement and consequently cause the chronic destruction of the joint (Dijkstra et al. 2019). Many studies have shown the presence of activated or cleaved complement components in the joint, and elements such as C1q–C4 complexes in the circulation of patients with RA (Dijkstra et al. 2019; Wouters et al. 2006). The level of C5a is elevated in the synovium of patients with RA, which is related to an increased number of infiltrating neutrophils. It seems that C3a and C5a are involved in the activation of the NLRP3 inflammasome pathway, which is important in RA inflammatory processes (Paoliello-Paschoalato et al. 2015) (Figs. 1, 2).

Some of the innate immunity-related targets for the treatment of RA are listed in Table 1 (US Food and Drug Administration (FDA) approved and clinical trials).

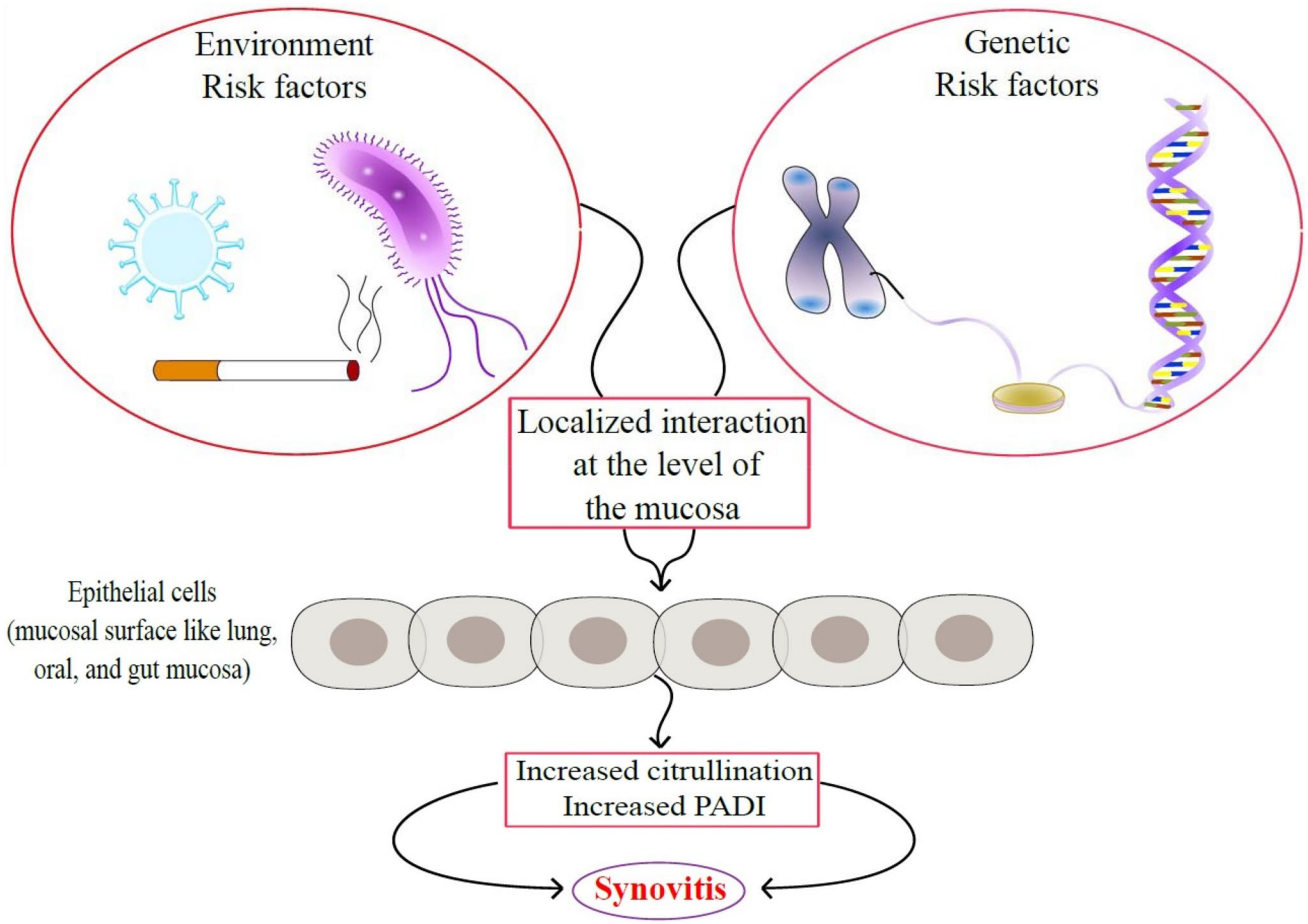

Fig. 1 Mucosal surfaces considered as potential initiating sites of RA. Environmental risk factors (smoking and infections) and various susceptibility genes lead to localized innate immune responses in epithelium, especially airway epithelial cells. This localization of innate immune cells results in some changes in epithelium, including induction of oxidative stress and expression of protein-arginine deiminase (PADI), with consequent generation of citrullinated proteins and synovitis in the latter

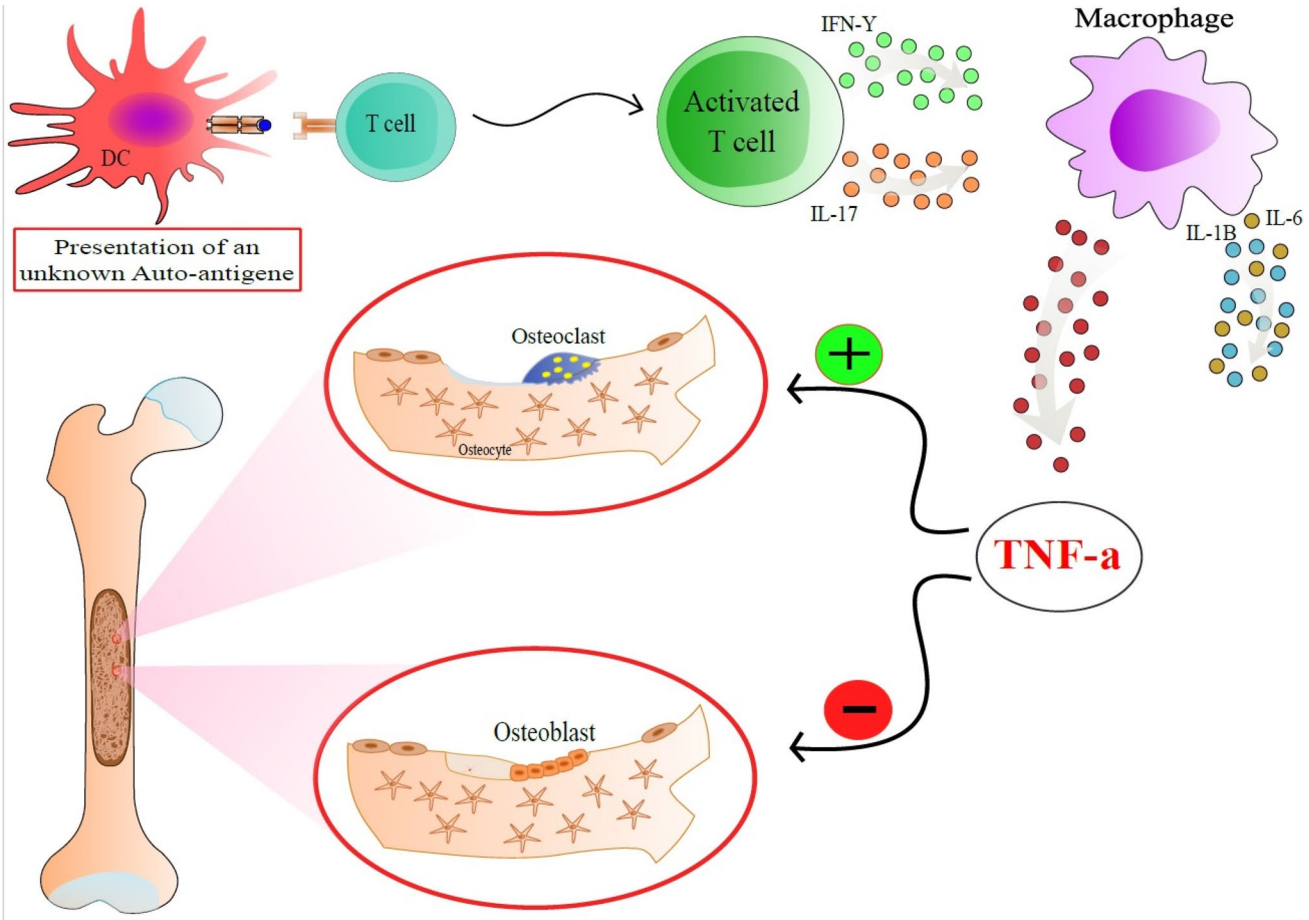

Fig. 2 Summary of innate immunity involved in the synovium. After the interaction between synovial $CD4^+$ T cells and antigen-presenting cell (APC) presenting an unknown antigen, T cells differentiate to Th1 and Th17 and produce IFNγ and IL-17, respectively. These cytokines stimulate synovial MQ to secrete proinflammatory mediators, among which TNFα is paramount. TNFα regulates the balance between bone destruction and formation under normal conditions. In RA disease, TNFα stimulates osteoclastogenesis and inhibits the differentiation of activated osteoblast

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE), also simply known as lupus, is a chronic multifaceted autoimmune disease with protean manifestation that affects multiple organs including kidneys, skin, heart, and lungs. It is characterized by the presence of specific autoantibodies for self-antigens, such as double-stranded DNA (dsDNA), ribonucleoproteins, histones, and certain cytoplasmic components (Herrada et al. 2019). Some studies have elucidated that various immune cells and proinflammatory cytokines play a significant role in SLE pathogenesis. The innate immune system, particularly MQs, have been indicated as a key player in the pathogenesis of SLE (Dema and Charles 2014). In this review, we focus on cellular and molecular components of innate immunity in SLE pathogenesis.

MQs are defective in the phagocytosis and clearance of apoptotic cells; thus, prolonged exposure of autoantigens to the adaptive immune cells provides survival signals for autoreactive B cells and consequently loss of tolerance to nuclear antigens released from apoptotic cells (Ma et al. 2019a; b). Plasticity is a major feature of MQs, which depends on cytokine milieu. MQs are classified as two main groups: classically activated MQs (M1) and alternatively activated MQs (M2). M1 MQs are induced by IFNγ and lipopolysaccharide (LPS) that are involved in inflammatory responses, whereas M2 MQs are induced by IL-4 and IL-13 that are involved in tissue remodeling (Chalmers et al. 2015; Labonte et al. 2014; Mantovani et al. 2004). Some data has suggested that M1 and M2 MQs have different roles in SLE development. M1 MQs increase the severity of the condition, while M2 MQs reduce it (Li et al. 2015). Therefore, MQ polarization modulates the development of SLE. It is reported that M2-polarizing cytokines such as IL-4 may have therapeutic effects to reduce SLE symptoms (Li et al. 2015).

Table 1 Therapies currently under investigation that target innate immunity components in RA

Drug	Target	Trial ID	Clinical stage	Mechanism of action	References
Adalimumab	TNFα	NCT00650026	FDA approved	Fully humanized anti-TNFα monoclonal antibody. Diminished inflammatory cell migration into joints following downregulation of CRP, IL-6, IL-8, CXCL5, CXCL9, CXCL10, and sTNFR2	Boisen et al. (2019), Eng et al. (2016), Mitoma et al. (2008), Ternant et al. (2015)
Etanercept	TNFα/β	NCT00094341	FDA approved	A recombinant fusion protein that consists of the soluble TNFα receptor (p75) linked to the Fc portion of human IgG1 which binds TNFα and TNFβ, downregulated serum levels of MMP-3 and MMP-1 in parallel with the reduction in CRP	Catrina et al. (2002), Dalakas and Hohlfeld (2003)
Golimumab	TNFα	NCT00973479	FDA approved	Human monoclonal antibody binds to TNFα, thereby preventing TNFα-mediated immune responses, e.g., reductions in levels of CRP, IL-6, MMP-3, ICAM-1, and VEGF	Food and Drug Administration (2009), Shealy et al. (2007)
Certolizumab pegol	TNFα	NCT01443364	FDA approved	Binds to soluble and membrane-bound TNFα, inhibiting the proinflammatory actions of this cytokine. Inhibits stimulated mast cell degranulation in vitro. Unlike other TNFi, it does not cause CDC and ADCC	FDA (2008), Nesbitt et al. (2007), Nesbitt et al. (2009)
Infliximab	TNFα	NCT00714493	FDA approved	Chimeric monoclonal antibody binds to both soluble and transmembrane TNFα and can reduce swollen joint and synovial inflammation, bone resorption, and cartilage degradation	Tournadre et al. (2012), Wijbrandts et al. (2008)
Tocilizumab	IL-6	NCT01119859	FDA approved	Humanized IgG1 monoclonal antibody binds soluble as well as membrane-bound IL-6 receptors, hindering IL-6 from exerting its proinflammatory effects	Ohta et al. (2014)
Tofacitinib	JAK1 and JAK3	NCT03976245	FDA approved	Prevents the activation of the JAK-STAT signaling pathway. Impairs the monocyte-derived DC differentiation	Kumamoto et al. (1996), Marzaioli et al. (2019)
Baricitinib	JAK1 and JAK2	NCT03915964	Phase IIII	Preferentially targets signaling receptors associated with JAK1 and JAK2. Modulates signaling pathway involved in the inflammatory response, decreased rate of chemotaxis toward IL-8 in neutrophil, abrogated invasion of FLS induced by IFNγ	Karonitsch et al. (2018), Mitchell et al. (2017)
Anakinra	IL-1	NCT00117091	FDA approved	Non-glycosylated recombinant form of the IL-1 receptor antagonist reduces the migration of inflammatory cells (such as intimal layer MQs and subintimal MQs and lymphocytes) into the joint	Cunnane et al. (2001)
Denosumab	RANKL	NCT00095498	Phase II	Humanized monoclonal antibody that binds to RANKL with high affinity and blocks RANK–RANKL association, and results in an impaired bone resorption by osteoclasts, decreased bone erosion and joint damage	Iwamoto et al. (2019)
Filgotinib	JAK1	NCT03025308	Phase III	Highly selective JAK1 inhibitor decreased IL-1β, IL-6, TNFα, SAA, GM-CSF	Taylor et al. (2017)
Upadacitinib	JAK1	NCT02675426	FDA approved	Selective JAK1 inhibitor, reversibly inhibited IL-6-induced pSTAT3	Mohamed et al. (2020)

Table 1 (continued)

Drug	Target	Trial ID	Clinical stage	Mechanism of action	References
Peficitinib	JAK1, JAK2, JAK3, and Tyk2	NCT01638013	Phase III	Suppressed phosphorylation of STAT1, STAT3, and STAT5 in RA FLS and also proliferation of FLS through inhibition of inflammatory cytokines	Ikari et al. (2019)
Vobarilizumab	IL-6R	NCT02518620	Phase II	Nanobody consisting of an anti-IL-6 receptor domain and an anti-human serum albumin domain	Dörner et al. (2017)
Sarilumab	IL-6R	NCT02332590	Phase III	Binds to both sIL-6R and mIL-6R and inhibits the IL-6-mediated proinflammatory cytokine produced by a variety of cell types including monocytes, and fibroblasts synovial and endothelial	Huizinga et al. (2014)

ADCC antibody-dependent cellular cytotoxicity, *CDC* complement-dependent cytotoxicity, *CRP* C-reactive protein, *DC* dendritic cell, *FDA* Food and Drug Administration, *GM-CSF* granulocyte–macrophage colony-stimulating factor, *ICAM* intercellular adhesion molecule, *Jak* Janus kinase, *MMP* matrix metallopeptidases, *MQ* macrophage, *sIL* soluble interleukin, *pSTAT* phosphorylated signal transducers and activators of transcription, *RANKL* receptor activator of nuclear factor kappa-B ligand, *SAA* serum amyloid A, *TNFi* tumor necrosis factor inhibitor, *Tyk* tyrosine kinase, *VEGF* vascular endothelial growth factor

Of circulating white blood cells, neutrophils are the largest in number. It is proposed that they play a pathogenic role in SLE. Patients with SLE have elevated numbers of apoptotic neutrophils in circulation; this scenario is related to the development of autoantibodies against DNA and disease activity (Herrada et al. 2019; Lande et al. 2011). Clearance of NETs is defective in patients with SLE and leads to the presentation of self-antigens, including immunogenic DNA, histones, and neutrophil proteins to the immune system and contributes to the development of autoantibodies and proinflammatory cytokines, driving the pathogenesis of SLE (Apel et al. 2018; Herrada et al. 2019). The neutrophils of patients with SLE have an abnormal function; their phagocytosis ability is decreased, while their production of ROS is increased (Alves et al. 2008). NETosis, a type of cell death, is elevated in the neutrophils of patients with SLE by the presence of antibody–ribonucleoprotein complexes, which activate various immune cells. Mouse models of SLE demonstrate elevated bone marrow NETosis and autoantibodies that distinguish NET components (Gupta and Kaplan 2016). It is reported that endonuclease DNase1 is required to degrade NETs. Some patients with SLE have DNase1 inhibitors, whereas other patients with SLE have high levels of antibodies that bind to NETs and protect them from DNase1 (Apel et al. 2018). A distinct subset of neutrophil-like cells termed low-density granulocytes (LDGs) are distinguished in patients with SLE that produce excess proinflammatory cytokines such as IL-6, IL-8, TNFα, and IFN-I. It is proposed that LDGs have an important role in SLE pathogenesis (Apel et al. 2018; Carmona-Rivera and Kaplan 2013).

Some studies documented dysregulated DCs play a critical role in the initiation and development of SLE (Mok 2015). DCs from patients with SLE show a considerable reduction of PD-L1 expression during active disease, whereas the expression of CD80/CD86 is elevated (Mackern-Oberti et al. 2015).

Plasmacytoid DCs (pDCs) in patients with SLE produce high levels of IFNα that causes a positive-feedback loop in the activation of innate and adaptive immunity (Mok 2015). pDCs numbers are decreased in the blood of patients with SLE, but pDCs nonetheless accumulate in the damaged skin of patients with lupus (Herrada et al. 2019). Several reports have indicated that pDCs depletion reduces the activation and expansion of immune cells, limits autoantibody production, and restricts kidney inflammation in patients with SLE (Rowland et al. 2014).

Increased IFNα levels in in patients with SLE are correlated with both disease activity and severity. Sustained IFNα production, a signature of lupus, may lead to the development of autoreactive T and B cells (Huang et al. 2011; Ronnblom and Alm 2001).

NK cells may have a crucial role in the pathogenesis of SLE. It has been reported that the number of NK cells in

patients with SLE is diminished and their cytotoxicity is impaired (Cho et al. 2011). Some studies have suggested a decrease in the number of natural killer T (NKT) cells in patients with SLE (Chen et al. 2015). IL-15 is a cytokine that plays a major role in NK differentiation and survival and was elevated in patients with SLE, a scenario which is related to disease activity (Lin et al. 2017). The activatory receptor CD69 is overexpressed in NK cells of patients with SLE with active disease (Lin et al. 2017). Some studies have indicated that NK cells produce high levels of IFNγ in patients with SLE with active disease and this has been associated with cytotoxicity and contributed to the dysregulation of the link between innate and adaptive immunity in SLE (Hervier et al. 2011).

Basophils are involved in skin lesions in patients with SLE and have a role in promoting tissue damage (Pan et al. 2017). Basophils are proposed as a biomarker of disease activity in SLE. These cells have an important role in inflammation and anti-nuclear antibody production by B cells (Charles et al. 2010). Prostaglandin D_2 (PGD_2) is increased in patients with SLE and interacts with PGD_2 receptors on the surface of basophils, leading to migration of basophils to secondary lymphoid organs (Pellefigues et al. 2018).

The complement system plays controversial roles in the pathogenesis of SLE. This system has protective and pathologic functions. Complement exerts its protective role through clearance of immune complexes and apoptotic cells, as well as induction of tolerance (Pabón-Porras et al. 2019). Complement activation leading to the inflammatory response and tissue damage defines the pathologic role of complement (Markiewski and Lambris 2007). Complement deficiency is correlated to the pathogenesis of SLE (Pabón-Porras et al. 2019). C1q deficiencies, including genetic defects or anti-C1q autoantibodies, can cause SLE in 90% of patients. It is well established that C1q is involved in the regulation of immune cell differentiation and MQ polarization to a tolerogenic phenotype (Son et al. 2015). The low levels of C1q, C4, and C2 are associated with dysfunction in the clearance of apoptotic and debris cells (Pabón-Porras et al. 2019).

Keratinocytes may be a key player in the pathogenesis of SLE. These cells are activated by UV light and produce inflammatory cytokines that result in the recruitment of immune cells and the initiation of inflammatory responses (Pentony et al. 2017) (Fig. 3).

Some of the innate immunity-related targets for the treatment of SLE are listed in Table 2 (clinical trials).

Sjögren's syndrome

Sjögren's syndrome (SS) is a systemic autoimmune disease that affects the exocrine glands, mainly involving the lachrymal and salivary ones, leading to dryness of the eyes and mouth. SS is classified into two forms: primary (pSS) and secondary (sSS). Primary SS is often associated with dysfunction in lacrimal and salivary flow and features a wide range of both organ-specific and systemic manifestations, whereas sSS occurs in association with another autoimmune disease, such as SLE or RA (Kiripolsky et al. 2017; Malladi et al. 2012). While the pathogenesis of pSS is currently not well understood like other autoimmune diseases, both innate and adaptive immune systems play a critical role in the disease pathogenesis. Many types of innate cells are implicated in SS.

Some studies have also shown that MQs are critical mediators of SS pathogenesis (Ma et al. 2019a; b). The presence of M1 and M2 MQs has been indicated in the salivary glands in the SS mouse model (Baban et al. 2013; Ma et al. 2019a, b). Proinflammatory M1 polarization is the major phenotype of SS MQ and systemic and local concentrations of IL-6 are importantly increased in patients with SS (Tishler et al. 1999). Also, patients with SS with more active disease display higher levels of IL-12, while patients with less active disease display higher levels of IL-35 (Fogel et al. 2018). Levels of monocyte chemoattractant protein-1 (MCP-1/CCL2), IFNγ, and proinflammatory cytokines or chemokines that are secreted by monocyte and MQ, such as, IL-6, IL-18, IFN-I, and BAFF, are importantly elevated in patients with SS (Hernández-Molina et al. 2011; Willeke et al. 2009; Brkic et al. 2013; Yoshimoto et al. 2011). It has also been reported that the level of IκBα in SS monocytes is decreased, which leads to NFκB signaling pathway dysregulation and production of proinflammatory cytokines (Lisi et al. 2012).

DCs play a significant role in SS, as they function as antigen-presenting cells in ectopic germinal centers in the salivary gland (Bombardieri and Pitzalis 2012). Some studies suggest that DCs are increased in salivary tissue of patients with pSS as compared to controls (Ozaki et al. 2010). Plasmacytoid DCs, a specific DC subset, are activated by Toll-like receptors (TLRs) and produce several proinflammatory cytokines, including IFNα (Vogelsang et al. 2006).

Primary DCs are the main source of IFN-I in response to foreign nucleic acids. IFN-I might be involved in the pathogenesis of SS (Hillen et al. 2019). Self-nucleic acids in the form of autoantibody complexes and apoptotic cell fragments are present in patients with pSS and considerably activate production of IFN-I by pDCs (Ainola et al. 2018). It is indicated that pDCs play a critical role in pSS pathogenesis (Hillen et al. 2019). The activated phenotype and enhanced production of proinflammatory cytokines by pSS-pDCs can affect salivary gland inflammation dramatically (Hillen et al. 2019).

Some studies have shown that NK cells are involved in SS pathogenesis, although the precise role of these cells is unknown. NK cells have been related to salivary

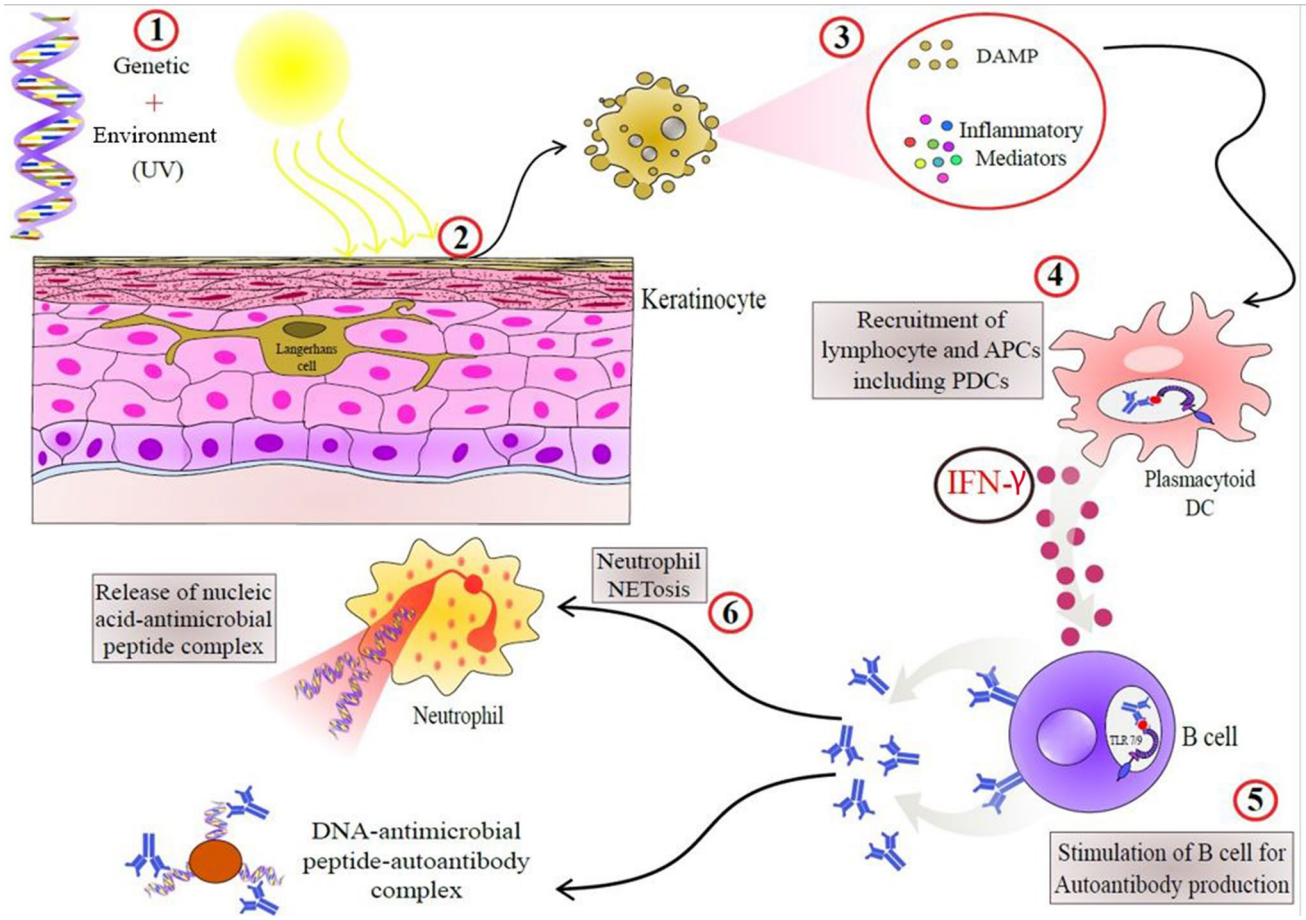

Fig. 3 Role of innate immunity in SLE pathogenesis. Genetic and environmental factors contribute to a breakdown of self-tolerance in SLE. Exposure to sunlight induces apoptosis of keratinocytes, leading to the formation of blebs which contain both nuclear and cytoplasmic antigens on the surface of dying cells. These antigens are captured by APC cells such as B cells and pDCs. Activated pDC produces abnormally large amounts of IFN-γ leading to more production of autoantibodies by B cells. Autoantibodies induce NETosis and the release of antimicrobial peptides results in nuclear antigen complex formation. The net result is a cycle of antigen release and immune activation that leads to the production of high-affinity autoantibodies

gland inflammation in patients with pSS. NK cells express NCR3/NKp30 that regulates IFN-II secretion and correlation with DCs. In patients with pSS, NKp30 expression is elevated in comparison to controls. Salivary gland epithelial cells express NKp30 ligand, and interaction of this ligand with NKp30 leads to the production of Th1 cytokines (Rusakiewicz et al. 2013). In contrast to the salivary gland, in patients with pSS, the number and activity of peripheral blood NK cells are significantly reduced as compared to healthy controls (Izumi et al. 2006). It is possible that NK cells are protective in early stages of the disease and later play a pathogenic role in advanced disease (Kiripolsky et al. 2017). It was proven that invariant natural killer T (iNKT) cells were significantly decreased in pSS, and a possible correlation between the low number of iNKT and autoreactive tissue injury was suggested (Rizzo et al. 2019).

It is known that in patients with SS, neutrophil functions such as phagocytosis, chemotaxis, and chemokinesis were normal, while their adherence ability was impaired (Gudbjörnsson et al. 1991).

Some studies have reported a significant role of salivary gland epithelial cells in SS pathogenesis (Kiripolsky et al. 2017; Manoussakis and Kapsogeorgou 2007). Furthermore, it has been shown that salivary gland epithelial cells express high levels of TLR2, TLR3, and TLR4; thus, they contribute to the induction of innate immune responses upon recognition of foreign pathogens (Deshmukh et al. 2009; Low and Witte 2011; Manoussakis and Kapsogeorgou 2007).

Some of the innate immunity-related targets for the treatment of Sjögren's syndrome are listed in Table 3 (clinical trials).

Table 2 Therapies currently under investigation that target innate immunity components in SLE

Drug	Target	Trial ID	Clinical stage	Mechanism of action	References
Venetoclax (ABT-199)	BCL-2	NCT01686555	Phase I	Targeted pDCs	Dalakas (1991), Felten et al. (2018)
BIIB059	BDCA2	NCT02847598	Phase II	Monoclonal antibody targeting blood DC antigen 2 is a pDC-specific therapy, inhibits the production of IFN-I when ligated	Chaichian et al. (2019), Hilton-Jones (2011)
Emapticap pegol (NOX-E36)	CCL2	NCT00976729	Phase I	Inhibition of the receptor axis CCL2/CCL2 by neutralization of the human chemokine CCL2	Felten et al. (2018), Shamim et al. (2000)
MRA 003 US	IL-6R	NCT00046774	Phase I	Disrupts IL-6 signaling	Dalakas and Hohlfeld (2003)
Ustekinumab	IL-12/23	NCT04060888	Phase III	Monoclonal antibody neutralizes IL-12- and IL-23-mediated functional responses	Behrens et al. (1998), Van Vollenhoven et al. (2018)
BT063	IL-10	NCT02554019	Phase II	Humanized monoclonal antibody, which selectively neutralizes human IL-10	Klavdianou et al. (2020)
AGS-009	IFNα	NCT00960362	Phase 1	Humanized mAb against a broad range of IFNα subtypes	Felten et al. (2018), Tcherepanova et al. (2013)
JNJ-55920839	IFN-I	NCT02609789	Phase I	Monoclonal antibody that binds to IFNα	Felten et al. (2018), Tews and Goebel (1996)
IFNα–kinoid	Active immunization with IFNα–kinoid	NCT02665364	Phase II	Therapeutic vaccine composed of IFNα2b coupled to a carrier protein which induces a polyclonal anti-IFNα response	Felten et al. (2019)
Tofacitinib	JAK1 and JAK3	NCT03288324	Phase I/II	Binds to JAK and prevents the activation of the JAK-STAT signaling pathway. This may decrease the production of proinflammatory cytokines, IFNα/β	Oon et al. (2016), Tournadre et al. (2012)
Baricitinib	JAK1 and JAK2	NCT03616964	Phase III	Selective and reversible inhibitor of JAK1/2 leads to the inhibition of the JAK-STAT signaling pathway. This decreases the IFN-responsive genes	Klavdianou et al. (2020), Oon et al. (2016)
Filgotinib	Highly selective JAK1	NCT03134222 (CLE)	Phase II	JAK1-selective inhibitor demonstrated reduction of proinflammatory cytokines	Klavdianou et al. (2020), Pohlmeyer et al. (2018)
BMS-986165	Tyk2	NCT03920267	Phase II	Highly potent and selective allosteric inhibitor of Tyk2. Blocks IL-12, IL-23, and IFN-I signaling	Gillooly et al. (2016), Klavdianou et al. (2020)
Iguratimod	NF-κB	NCT02936375	Phase II	Inhibited nuclear translocation of NF-κB p65 and inhibit MIF-induced proinflammatory effects, including monocyte cytokine release	Jiang et al. (2020), Klavdianou et al. (2020)
OMS721	MASP-2	NCT02682407	phase II	Humanized monoclonal antibody that inhibits MASP-2; the effector enzyme of the lectin pathway inhibits MASF-2 that cleaves C4 and C2	Eloranta et al. (2007), Felten et al. (2018)

Table 2 (continued)

Drug	Target	Trial ID	Clinical stage	Mechanism of action	References
RSLV-132	Autoantibody-bound RNA	NCT02660944	Phase II	Fully human Fc fusion protein comprising human RNAse fused to the amino terminus of the Fc domain of human IgG1. It digests autoantibody-bound RNA, preventing autoantibodies from stimulating intracellular inflammatory pathways	Klavdianou et al. (2020)

BCL B cell lymphoma, *BDCA* blood dendritic cell antigen, *CCL* chemokine ligand, *CLE* cutaneous lupus erythematosus, *DC* dendritic cell, *IL* interleukin, *Jak* Janus kinase, *MASP* mannan-binding lectin-associated serine protease, *MIF* macrophage migration inhibitory factor, *pDC* plasmacytoid dendritic cell, *STAT* signal transducers and activators of transcription, *Tyk* tyrosine kinase

Polymyositis

Polymyositis (PM) is an unusual chronic inflammatory connective tissue disease that involves muscles that undergo atrophy over time, so patients with PM cannot climb stairs or even walk. Muscle involvement is different in different parts of the body, and muscle weakness can lead to problems for patients such as dysphagia and breathing difficulties. PM is an autoimmune disease with no clear etiology. As with the other autoimmune conditions, PM is more common in women (Dalakas 1991; Dalakas and Pongratz 2003; Hilton-Jones 2011). Genetics is likely to be associated with the disease, and the presence of specific human leukocyte antigen (HLA) genes such as *DRB1*0301* alleles increases the likelihood of PM (Shamim et al. 2000). PM is strongly associated with other inflammatory, viral, and cancerous diseases (Dalakas and Hohlfeld 2003; Hill et al. 2001). Although muscles do not usually express MHC I, they express MHC I and even MHC II widely in PM. Cytotoxic T cells (CTLs) attack healthy fibers of muscles which express MHC I, which seems to be the main reason for tissue injury. Upregulation of co-stimulatory molecules helps the activation of CTLs, but not classic co-stimulatory molecules. Muscles have their own co-stimulatory molecules called BB-1 (Behrens et al. 1998). Muscle biopsies show CTLs migrating into the basal lamina where they accumulate to attack muscle fibers (Arahata and Engel 1986). The mechanism by which fibers are destroyed is via perforin and granzyme, yet muscle fibers express Fas (Behrens et al. 1997). There is little evidence of innate immunity involvement in the immunopathology of PM.

Many inflammatory cytokines are increased in serum of patients with PM, such as IL-1, IL-2, IL-6, and IL-10 as well as TNFα, IFN-γ, and TGFβ (Tews and Goebel 1996). IL-1 and TNFα have a devastating effect on muscles; TNFα induces a proteolytic effect via glucocorticoids, whereas IL-1β exerts its effect through an independent glucocorticoid pathway (Zamir et al. 1992). Overexpression of chemokines has also been observed, including CXCL8, CCL9, CCL2, CXCL9, and CXCL10. They help in directing T cells to the inflammatory sites such as endomysial in inflammatory cells (De Bleecker et al. 2002).

Increased TLRs were observed in biopsies from myopathies, especially TLR3 and TLR7, which are activated by the nucleic acids. Necrotic muscle cells can activate TLR3 which triggers the production of a large amount of IL-6 from myoblasts, leading to the maintenance of inflammatory response in the muscles (Tournadre et al. 2012).

High mobility group box 1 protein (HMGB1) is a nuclear protein that can be secreted by immune cells in inflammatory conditions (Harris et al. 2012). It is secreted

Table 3 Therapies currently under investigation that target innate immunity components in Sjögren's syndrome

Drug	Target	Trial ID	Clinical stage	Mechanism of action	References
Iguratimod	NF-κB	NCT03023592	Phase II	Preventing activation of the NF-κB signaling pathway	NIH (2020i), van den Hoogen et al. (2020)
Filgotinib	JAK1	NCT03100942	Phase II	Janus kinase inhibitor with selectivity for subtype JAK1	Dalakas and Hohlfeld (2003)
Parsaclisib	PI3Kδ	NCT03627065	Phase II	Potent and highly selective (PI3Kδ) inhibitor	Dalakas and Pongratz (2003), Gandolfo and De Vita (2019)
VIB7734/MEDI7734	ILT-7	NCT03817424	Phase I	mAb against ILT-7 downregulates IFN production by causing the depletion of pDC	van den Hoogen et al. (2020)
CFZ533/iscalimab	CD40	NCT02291029	Phase II	Blocking, non-depleting anti-CD40 antibody	Gandolfo and De Vita (2019)
RSLV-132	Circulating RNA complexed	NCT03247686	Phase II	Mono-specific nuclease Fc fusion protein that consists of human RNase attached to the Fc portion of IgG. The aim is to reduce the levels of circulating RNA-containing immune complexes	Mavragani and Moutsopoulos (2019)
Ustekinumab	IL-12/23	NCT04093531	Phase I	Monoclonal antibody directed against the p40 subunit, therefore blocking the biologic activity of IL-12 and IL-23 simultaneously	Sambataro et al. (2017)

IL interleukin, *ILT* immunoglobulin-like transcript, *Jak* Janus kinase, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *PI3K* phosphoinositide 3-kinase

by MQs and DCs in connective tissue and enhances MHC I expression by binding to TLR4 in muscle fibers (Ulfgren et al. 2004).

The role of eosinophils in myopathies has also been established; patients who have eosinophilia in muscle biopsy, especially endomysium, have more necrotic fibers (Kumamoto et al. 1996).

DCs accumulate in muscle tissue to present antigens, and plasmacytoid DCs secrete IFN-I (Eloranta et al. 2007). IFN-I plays an essential role in PM. One of the mechanisms that lead to IFN secretion is via cathelicidins, which include LL-37, which is the only cathelicidin expressed in humans. Along with all its antimicrobial, anti-inflammatory, and even proinflammatory functions, LL-37 increases IFN-I (Hilchie et al. 2013). LL-37 footprints have been seen in inflammatory and autoimmune diseases (Kahlenberg and Kaplan 2013). Continuous immune system contact with IFN-I can cause immune tolerance failure and autoimmune diseases, such as myositis (Lu et al. 2017).

Systemic sclerosis

Systemic sclerosis (SSc, scleroderma) is a chronic, heterogeneous autoimmune disease. Thickening of the skin, fibrosis of connective tissue, and vessel dysfunction are results of excessive collagen secretion from the fibroblasts and its deposition which can sometimes involve internal organs (Dowson et al. 2017). Myofibroblasts are the active form of fibroblasts which secrete collagen persistently and is found in fibrotic lesions (Artlett et al. 2011). The main cause of SS is still unclear but the immune system has an important role and autoantibodies are found in most patients. T cells, especially Th2, interact with fibroblasts through profibrotic cytokines such as IL-4, IL-6, and IL-13, which results in aggravation of fibrosis (O'Reilly et al. 2012). The innate immune system plays a critical role in both the onset and progression of the disease (Pattanaik et al. 2015).

The role of many pattern recognition receptors (PRRs) has been proven in autoimmune diseases (Duffy and O'Reilly 2016), such as TLRs in SSc. TLRs identify damage-associated molecular patterns (DAMPs) that have been released from endogenous cells, e.g., they may be secreted in response to stress or damage; also the response of TLRs to PAMPs that leads to the activation of an intracellular signaling pathway, and the improper and over-response of the TLRs to their ligands can be involved in the onset and exacerbation of the disease (Ciechomska et al. 2013a, b). $CD14^+$ monocytes and DCs are activated by TLR4, resulting in a large amount of CCL8 and IL-10 secretion in patients with SSc. CCL8 and IL-10 are chemoattractants of T cells and fibrotic factors which increase in the serum of patients with scleroderma (van Lieshout et al. 2009). Serum amyloid A (SAA), which is a ligand for TLR2 and a type of DAMPs

family, can be elevated in patients with scleroderma. This pathway leads to the production of IL-6 through NF-κB (O'Reilly et al. 2014a, b), and IL-6 directly increases collagen secretion from fibroblasts (O'Reilly et al. 2014a, b). Differentiation of fibroblasts into myofibroblasts is common in patients with scleroderma, which results in increased TLR9 because 60% of myofibroblasts express TLR9 (Fang et al. 2016). When TLR9 is activated by its ligand, CpG, secretion of TGFβ would increase. TGFβ has a major role in the differentiation of myofibroblasts and the production of collagen (Fang et al. 2016). MyD88 has a key role in TLR signaling and SSc pathogenesis, and researchers could decrease fibrogenesis by inhibiting MyD88 (Singh et al. 2012).

Monocytes are important cells in SSc. These cells have an important role in extracellular matrix (ECM) remodeling in patients with SSc through TLR8 (ssRNA) and tissue inhibitor of metalloproteinase-1 (TIMP-1) secretion (Duffy and O'Reilly 2016). Fibroblasts break down ECM by secreting matrix metalloproteinase-1 (MMP-1) and maintaining homeostasis; TIMP-1 inhibits MMP-1 and leads to the accumulation of ECM in patients with SSc (Ciechomska et al. 2013a, b). The number of monocytes and MQs elevates in the peripheral blood and the inflammatory sites in patients with scleroderma; this makes the situation worse because these cells are resistant to apoptosis (López-Cacho et al. 2014), and releasing fibrotic factors (Higashi-Kuwata et al. 2010). It has also been reported that IL-4, IL-13, and IL-10 are higher than normal in the serum of patients with scleroderma (Scala et al. 2004), and this causes the formation of M2 MQs, which means more TGFβ and more fibrosis (Higashi-Kuwata et al. 2010).

For years, researchers have been trying to find a link between SSc and the increase or decrease in complement components. It seems that the presence of autoantibodies helps to activate the complement and activation factors increase in all three pathways (Okrój et al. 2016). Vascular endothelium damage is a common cause of scleroderma, which seems to be an important item in the induction of the disease. Factor H is a regulator of complement and its principal function is to protect host cells against complement. Host cells may be damaged by dysfunction of factor H and release cellular contents, react with existing autoantibodies, and form immune complexes (Scambi et al. 2010).

The inflammasome is a multi-factor assembly which is mainly activated by TLRs that lead to activated caspase-1, resulting in IL-1β and IL-18 activation by caspase-1. NLRP3 is the best-known inflammasome and has the main role in many autoinflammatory and autoimmune diseases (Martinon et al. 2002). The role of the IL-1β and IL-1α has been confirmed in fibrosis by an autocrine effect on fibroblasts (Zhang et al. 2014), and serum levels of IL-1β are higher in patients with SSc than in healthy controls (Hussein et al.

Table 4 Therapies currently under investigation that target innate immunity components in SSc

Drug	Target	Trial ID	Clinical stage	Mechanism of action	References
Anifrolumab (MEDI546)	Directed against subunit 1 of IFN-I receptor	NCT00930683	Phase I	Downregulation of activation of T cells	Sierra-Sepúlveda et al. (2019), NIH (2020k)
MEDI7734	ILT-7	NCT02780674	Phase I	Transient degradation of pDC	NIH (2020e)
Tocilizumab	IL-6R	NCT01532869	Phase III	Regulatory function in the balance between Th17 and regulatory T cells	NIH (2020j)
AM095 and SAR100842	LPA1	NCT01651143	Phase II	Targets unique receptors connected to G proteins	NIH (2020f)
Imatinib	PDGF, TGFβ	NCT00555581	Phase II	Blockade both PDGF and TGFβ	NIH (2020c)
Dasatinib	c-Abl, PDGF	NCT00764309	Phase II	Second-generation TKIs with more significant Bcr-Abl affinities	NIH (2020g)
Nilotinib	c-Abl, PDGF	NCT01166139	Phase II	Second-generation TKIs with higher Bcr-Abl affinity	NIH (2020d)
Metelimumab	TGFβ	NCT00043706	Phase II	Particularly neutralizes isoform TGFβ1	NIH (2020h)
Fresolimumab	TGFβ1, β2, β3	NCT01284322	Phase I	Appears to be going for all TGFβ isoforms	NIH (2020b)
P144	TGFβ1	NCT00574613	Phase II	Disables the interaction of the TGFβ and TGFβ receptor type III	NIH (2020a)
Nintedanib	VEGF, PDGF, FGF	NCT02597933	Phase III	TKI targeting FGF, PDGF, and VEGF receptors, and also tyrosine kinases in the Src family	NIH (2020l)

FGF fibroblast growth factor, *IL* interleukin, *ILT* immunoglobulin-like transcript, *LPA* lysophosphatidic acid, *PDGF* platelet-derived growth factor, *TGF* transforming growth factor, *TKI* tyrosine kinase inhibitor, *VEGF* vascular endothelial growth factor

2005). Contrary to all efforts, the role of IL-18 has not yet been elucidated in the pathogenesis of SSc (Pan et al. 2011). IL-18 seems to have an antifibrotic effect unlike IL-1β (Kim et al. 2010) but it is increased in patients with SSc (Lin et al. 2019).

The mast cell accumulation has been seen in the affected skin of patients with SSc and has an important role in diseases associated with fibrosis (Hügle 2014) because mast cells have dense granules that contain proinflammatory cytokines, TGFβ, and histamine which help to form myofibroblasts. Mast cells and myofibroblasts interact through gap junctions or send vesicles and help each other to increase inflammation (Hugle et al. 2012).

Some of the innate immunity-related targets for the treatment of SSc are listed in Table 4 (clinical trials).

Conclusion

There is a great unmet need to identify how autoimmunity can be initiated, progressed, and propagated. In this context, innate immunity acts as both a provider of inflammatory conditions for adaptive immunity function and as an independent part or co-player to the adaptive immune system. The dysregulation of innate immunity has been shown in many disorders, so manipulation of related pathways has so far drawn attention, as far as the targeting of TNFα has revolutionized management and outcomes of RA disease. Also, a large number of other therapies are currently being tested in clinical trials; however, there is still much to be learned about this issue and related misconceptions.

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Compliance with ethical standards

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