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Review Article

The contribution of macrophages to systemic lupus erythematosus

Chunyan Ma[a], Yu Xia[a], Qingrui Yang[b,*], Yueran Zhao[a,*]

[a] Department of Central Laboratory, Shandong Provincial Hospital affiliated to Shandong University, Jinan 250021, China
[b] Department of Rheumatology and Immunology, Shandong Provincial Hospital affiliated to Shandong University, Jinan 250021, China

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ABSTRACT

As a heterogeneous autoimmune disease associated with severe organ damage, the precise mechanisms of systemic lupus erythematosus (SLE) remain to be clarified. Recent research indicates that innate immunity plays vital roles in SLE. Defects in the phagocytosis of apoptotic cells, aberrant activation and imbalanced polarization of macrophages, have been shown to participate in the pathogenesis of SLE. Treatments targeting these processes may ameliorate the disease activity in lupus models as well as in patients with SLE. Macrophages participate in the initiation of autoimmunity and the development of SLE in multiple levels. Better understanding of this complex disease is the prerequisite for exploring more effective therapies of SLE.

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease which can affect many organ systems. The etiology of SLE is still unclear up to now. It is broadly accepted that both genetic and environmental factors participate in the pathogenesis of SLE. The hallmarks of SLE include chronic inflammation and the production of many kinds of autoantibodies to self antigens. There are aberrant activations both in humoral and cellular immunity in SLE. In addition, recent investigations have highlighted the involvement of macrophages in SLE. Patients with SLE show monocyte/macrophage defects involving surface protein expression, cytokine production, and phagocytic capacity, indicating a role of innate immunity in the pathogenesis of SLE [1].

Abnormalities in cell death have been demonstrated in patients with SLE, including enhanced apoptosis, necrosis, and autophagy [2]. Immune cells in peripheral blood mononuclear cells (PBMCs) and cutaneous lesions from SLE patients show increased apoptosis [3,4]. Higher intrinsic DNA damage has been detected in PBMCs from lupus nephritis (LN) patients, which may contribute to the enhanced apoptosis [3]. On the other hand, macrophages from SLE patients show defects in clearance of apoptotic cells (ACs). The ACs uncleared efficiently may release autoantigens and activate the autoreactive B cells, resulting in loss of tolerance to autoantigens as well as production of autoantibodies [5]. Then the resultant immune complex (IC) deposition causes tissue injuries in different organs affected. The main functions of the macrophages include phagocytosis and subsequent antigen presentation. Moreover, macrophages have well-developed secretory functions and serve as an important source for a variety of cytokines, by which macrophages participate in inflammation and the modulation of adaptive immunity [6]. Both imbalanced polarization and abnormal activation of macrophages underlie the development of SLE. However, the roles macrophages playing in SLE remain to be elucidated. In the present review we will focus on the new advances about macrophages in SLE.

1.1. Type I interferon and macrophage function

It is accepted that defective clearance of ACs exists in SLE, resulting in increased release of self antigens. Marginal zone macrophages (MZMs) surrounding the splenic follicles play a crucial role both in the efficient clearance of ACs and in the induction of tolerance to autoantigens. The interaction between lymphotoxin β receptor on MZMs and membrane lymphotoxin (mLT) on the surface of MZ B cells, is essential for the maintenance of MZMs numbers and phagocytic function. In lupus spleens, however, plasmacytoid dentritic cells (pDCs) accumulate at the perifollicular region and produce IFN-α, which induces the migration of mLT+ B cells to the follicles. This results in the compromised MZMs numbers and function, consequently defective ACs clearance and loss of tolerance to self-antigens. Moreover, MZ B cells in the follicles interact with follicular dentritic cells (FDCs) and T follicular helper (Tfh) cells, and induce germinal center (GC) reactions to stimulate autoantibody production. High mobility group box protein 1 (HMGB1) and receptor for advanced glycation end-products (RAGE) form an autocrine loop modulating the maturation of pDC and type I interferon (IFN) secretion [7]. Type I IFN inhibits the clearance of ACs, induces plasma cells to produce autoantibodies [8]. The ICs containing

* Corresponding authors.
E-mail addresses: qryang720@163.com (Q. Yang), yrzhao@sdu.edu.cn (Y. Zhao).

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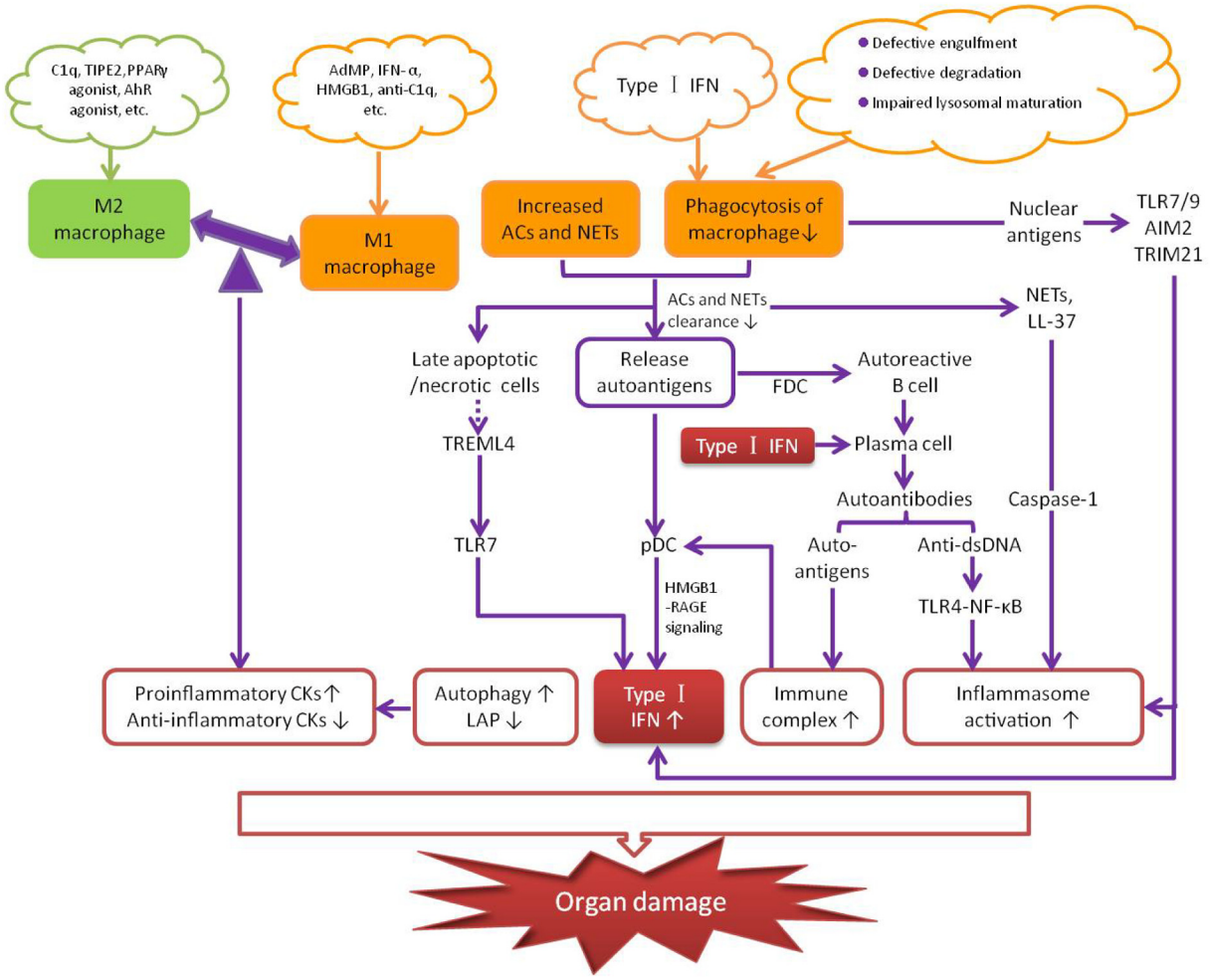

Fig. 1. Overview for the multiple roles of macrophages in the pathogenesis of systemic lupus erythematosus (SLE). Increased formation of apoptotic cells (ACs) and neutrophil extracellular traps (NETs), and defective phagocytic function of macrophage lead to the breakdown of immune homeostasis. The autoantigens released by uncleared ACs and NETs may induce autoreactive B cells proliferation and differentiation to produce autoantibodies, which participate in the formation of immune complex and tissue injuries. Both autoantigens and immune complex promote the production of type I interferon (IFN) by activating plasmacytoid dentritic cell (pDC). Anti-dsDNA antibodies activate inflammasome through toll-like receptor 4 (TLR4) -NF-κB pathway while NETs and LL-37 trigger inflammasome activation via caspase-1 signaling in macrophages. In addition, combined activation of TLRs and cytosolic sensors, absent in melanoma 2 (AIM2) and tripartite motif containing 21 (TRIM21), increases inflammasome formation and contributes to type I IFN secretion in macrophages. Furthermore, TREM-like transcript 4 (TREML4) may potentiate TLR7 signaling and type I IFN production in macrophages, even though the TREML4 ligand remains elusive. Type I IFN can induce plasma cells to produce more autoantibodies and inhibit the clearance of ACs by macrophages. Besides that, aberrant polarization, enhanced autophagy activation and impaired noncanonical autophagy (LC3-associated phagocytosis, LAP) of macrophages, may lead to increased proinflammatory cytokines (CKs) as well as decreased anti-inflammatory CKs. All above may contribute to the pathogenesis of SLE. TIPE2, TNF-α-induced protein 8-like 2; PPARγ, peroxisome proliferator activated receptor-γ; AhR, aryl hydrocarbon receptor; AdMP, AC-derived membrane microparticles; HMGB1, high mobility group box protein 1; LL-37, a cationic cathelicidin synthesized by neutrophils; FDC, follicular dentritic cell; RAGE, receptor for advanced glycation end-products.

antinuclear autoantibodies (ANAs) could stimulate pDC to produce more type I IFN to initiate the pathogenesis of SLE [9]. Type I IFN has been considered as the central pathogenic cytokine in SLE development [10]. The multiple roles of macrophages in the production of Type I IFN is shown in Fig. 1. Genetic susceptibility involved in the pathogenesis of SLE includes genes encoding components of upstream and downstream of type I IFN signaling, intracellular DNA degradation, and autophagy-related genes, all of which might enhance IFN-α production by pDC [11].

Accumulating data show that activated macrophages infiltrating kidneys mediate the aggressive adaptive immune response of SLE in mice [12–14]. It is accepted that HMGB1 contributes to the pathogenesis of SLE [15,16]. In addition to the modulation of type I IFN secretion by pDC, HMGB1 aggravates the severity of SLE via facilitating macrophage inflammatory response which is mediated by RAGE [16]. HMGB1 has been shown to associates with IL-1β, and the complex has greater proinflammatory activity than IL-1β alone [17]. Moreover, HMGB1 can function in a synergistic fashion with toll-like receptor (TLR) 2 ligand (PGN), TLR4 ligand (LPS), to activate mitogen-activated protein kinases (MAPKs) and NF-κB, resulting in upregulation of inducible nitric oxide synthase (iNOS) and nitric oxide (NO) via increased expression of multiple surface receptors (TLR2, TLR4 and RAGE) [18]. NO plays important roles in autoimmune processes.

RNA-seq study of SLE monocytes had revealed a distorted transcriptome, with transcription factors such as interferon regulatory factor (IRF) 1 and IRF2 functioning as potential regulators. Endotoxin has been demonstrated to induce type I IFN and patients with SLE exhibit increased circulating endotoxin. IRF1 and IRF2 may integrate inflammatory and interferon signals [19].

1.2. Defective phagocytosis of macrophage in SLE

1.2.1. Defective engulfment function of macrophage in SLE

Macrophages from healthy donors usually engulf and process

apoptotic material in a noninflammatory manner and the process for ACs clearance is transient. One of the best-known consequences of ACs clearance is immunosuppression, while the necrotic death is inflammatory. To achieve the anti-inflammatory effects ACs must be cleared efficiently by professional phagocytes on time to prevent these cells from undergoing secondary necrosis [20].

In SLE patients the engulfment dysfunction of ACs by macrophages has been identified. Macrophages containing ACs or AC fragments, also being called tingible body macrophages, accumulate in GCs within secondary lymphoid organs after the peak of an immune response when almost 10% of plasma cells undergo apoptosis [21]. The number of tingible body macrophages is significantly reduced in SLE patients. Consequently, nuclear autoantigens not properly cleared bind to FDCs and may thus provide survival signals for autoreactive B cells resulting in the loss of tolerance to nuclear antigens [22]. In addition, decreased production of anti-inflammatory signals during phagocytosis of ACs by macrophages also contributes to the initiation of an autoimmune response [6].

At first step of engulfment, ACs release “find-me” signals to attract phagocytes through activity of the apoptosis executioner caspases, caspase-3 and caspase-7. Partial hydrolysis products of plasma membrane phosphatidylcholine, lysophosphatidylcholine (LPC), sphingosine-1-phosphate (S1P), nucleoside triphosphates, as well as chemotactic factors such as fractalkine/CX3CL1 packaged into microparticles that are released upon apoptosis, all are examples for “find-me” signals [23,24]. Among these, LPC participates in the phagocytosis by forming a concentration gradient. Patients with SLE show significantly elevated LPC serum levels. High LPC concentration surrounding a dying or dead cell interferes with the build-up of the local LPC gradient and may contribute to impaired phagocytosis of ACs in SLE [25]. S1P, another find-me signal, is generated from sphingosine by sphingosine kinase 1 during apoptosis [26,27]. Watson L. et al. reported an increased serum concentration of S1P in juvenile-onset SLE patients [28]. Dying cell-released S1P may activate macrophage EPO signaling. EPO then potentiates ACs clearance through upregulation of peroxisome proliferator activated receptor-γ (PPARγ). Erythropoietin receptor (EPOR)-deficient macrophages show impaired ACs phagocytosis. In addition, macrophage-specific $EPOR^{-/-}$ mice develop lupus-like disease, and activation of EPO signaling ameliorates the disease progression in lupus-like mice. Therefore, S1P-EPO-PPARγ pathway plays crucial roles in ACs clearance by macrophages [29]. On the other hand, EPO also has been found to suppress inflammatory gene expression in macrophages [30].

After find-me step, ACs are recognized by phagocytes through “eat-me” signals including exposed phosphatidyl-serine (PS) at the outer leaflet of ACs plasma membrane [31]. Meanwhile, efficient removal of ACs also depends on opsonizing proteins such as IgM, mannose-binding lectin (MBL), serum amyloid P (SAP), C-reactive protein (CRP), and complement component C1q [32]. At last, receptors such as Stabilin-2, brain specific angiogenesis inhibitor 1 (BAI1) and T-cell immunoglobulin domain-containing 4 (TIM4)], TIM1 can bind directly to the exposed PS on ACs and mediate engulfment [33]. Besides that, the family of receptor tyrosine kinases such as TYRO3, Axl and Mer (TAM), can bind indirectly to PS through bridge molecules such as milk fat globule epidermal growth factor 8 (MFG-E8), growth arrest-specific gene 6 (Gas6), protein S or C1q [34,35]. Not all engulfment of ACs depends on exposed PS. Phagocytic receptor CD36 may link macrophages to ACs with thrombospondin-1 acting as a bridge molecule [36]. Research from Yamaguchi H et al. showed that some childhood-onset and adult SLE patients had a high circulating level of MFG-E8. Notably, they found the effect of MFG-E8 on engulfment was dose-dependent. At low concentrations, MFG-E8 promoted engulfment by forming a bridge between PS on ACs and integrins on macrophages, whereas at high concentrations, MFG-E8 may block the association due to saturating effect of MFG-E8 molecules to the binding sites [37]. In addition, glucocorticoids may enhance clearance of ACs by macrophages through transactivation of MFG-E8 expression [38].

Investigation on the expression of certain apopto-phagocytic genes in monocyte-differentiated macrophages from SLE patients shows decreased expression of molecules participating in ACs recognition, such as C1q, MFG-E8, and Gas6, which perturbs the prompt recognition of ACs [39]. Of note, C1q deficiency has been demonstrated to be the strongest known genetic link to autoimmunity associated with lupus [40,41]. C1q is predominantly produced in vivo by peripheral tissue macrophages and dendritic cells [42,43]. Murine macrophages triggered by LPS and ICs continuously secrete C1q [44]. C1q may facilitate the engulfment of ACs by bridging ACs and macrophages with its globular heads to ACs and its collagen tails to phagocytic receptors [45,46]. C1q upregulates a number of genes encoding well-characterized proteins related to engulfment of ACs. These proteins include C1q, C3, MFG-E8, Mer and the Mer ligands Gas6 [47].

Mer plays critical role in the engulfment and efficient clearance of ACs. Primary macrophages isolated from Mer(kd) mice showed phagocytic deficiency restricted to ACs which was independent of Fc receptor-mediated phagocytosis [48]. While C1q elicited enhanced engulfment of ACs in wild-type macrophages, macrophages from Mer-deficient mice failed to respond to C1q with enhanced engulfment of ACs. Moreover, C1q-dependent engulfment of ACs was inhibited by soluble Mer, which functioned as a decoy receptor for Mer ligand, Gas6. The inhibition of Gas6 then led to defective macrophage-mediated engulfment of ACs [47,49].

At last, the engulfment of ACs depends on rearrangement of actin cytoskeleton to form the phagosome and transferring dead cell cargo to lysosomes [50]. Activation of Rho family GTPases regulates actin dynamics in macrophages. During engulfment, activated Rac1 is recruited to form phagocytic cups at the selective lamellipodial sites of phagocytes. Once AC sinks into the cup, Rac1 is inactivated, resulting in breakdown of the phagocytic cup as well as AC engulfment [51]. Osteopontin (OPN) secreted by follicular CD153+ senescence-associated T cells in GCs may interfere with phagocytosis of ACs specifically captured via MFG-E8. In lupus-prone mice OPN secreting cells accumulated in the GCs. OPN induced prolonged Rac1 activation in phagocytes via integrin $\alpha_v\beta_3$ and hindered the dissolution of phagocytic actin cup, causing defective ACs engulfment [52].

Autoantibodies from SLE patients can modify the function of macrophages [53–56]. Anti-C1q antibody is present in 20–50% of patients with SLE, and has been found to be closely associated with renal involvement [57]. Anti-C1q antibody downregulates the endocytosis and phagocytosis rates in human monocyte-derived macrophages (HMDMs), maybe in part, due to decreased Mer expression [54]. It has been confirmed that efficient uptake of ACs by HMDMs is Mer dependent [58].

The clearance of ACs actively creates an anti-inflammatory milieu through secretion of cytokines such as transforming growth factor β (TGF-β) and interleukin-10 (IL-10), by macrophages. Both of them can further inhibit recruitment of macrophages at the site of dying cells and decrease secretion of proinflammatory cytokines [59–61].

1.2.2. Defective degradation of engulfed ACs and NETs

AC chromosomal DNA can be fragmented by cell-autonomous and macrophage-dependent mechanisms [62]. Decreased levels of DNASE I and DNASE II in macrophages might result in the accumulation of fragmented DNA and the production of inflammatory cytokines [39]. DNASE II is a lysosomal enzyme expressed in various types of cells, with prominent expression in macrophages [63]. DNASE II cleaves the DNA of engulfed ACs. DNASE $II^{-/-}$ macrophages may produce type I IFN via TLR-independent manner when they engulfed ACs, due to the inability of degradation of DNA [64].

Other enzymes including RNASE and DNASE critical for nuclear antigens degradation independent of lysosomes also have been demonstrated to participate in SLE [65–68]. As a Ca^{2+}/Mg^{2+} - dependent endonuclease secreted by a variety of endocrine and exocrine

glands [69], DNASE I is the principal nuclease found in serum and urine [70]. Reduced DNASE I activity has been found in patients with SLE [67]. Silencing of renal DNASE I is a unique renal feature of membranoproliferative LN [71]. DNASE I facilitates the breakdown of chromatin during apoptosis. DNASE1L3, a circulating DNASE produced primarily by macrophages and DC, has been linked to familial and sporadic SLE. DNASE1L3 participates in the digestion of the genomic DNA in AC-derived membrane-bound vesicles called microparticles. DNASE1L3-deficient mice develop anti-DNA autoantibodies and features of SLE [72]. Microparticles may contribute to the pathogenesis of SLE via binding to IgG to form a type of IC [73].

Except for apoptotic and necrotic cell remnants, neutrophil extracellular traps (NETs) might be another source of autoantigens and immunostimulatory damage-associated molecular patterns in SLE [74]. Activated neutrophils release chromatin and granule proteins to form extracellular fibers, NETs. The process of NETs clearance by macrophages resembles that of ACs, which is facilitated by extracellular preprocessing of NETs by DNASE I, as well as by the opsonization of NETs with C1q. The degradation of NETs occurrs in the lysosomal compartment and it is immunologically silent without production of proinflammatory cytokines [75]. Some NET-bound proteins, including HMGB1, LL-37, C1q, and anti-chromatin autoantibodies, may prevent the access of DNASE I to NETs [32]. Defective phagocytosis of macrophage in SLE also results in an impaired NETs degradation and prolonged half-life of NETs components. NETs proteins, such as LL-37, histones, dsDNA, neutrophil defensin, catalase, and annexin A1, provide autoantigens in SLE [76]. Protein modifications in uncleared ACs or NETs, including specific histone modifications as well as proteolytic cleavage of histones and other chromatin-associated proteins, generate neoantigens with increased antigenic and immunogenic potentials [32]. NETs internalisation by macrophages in SLE is a proinflammatory process companied with enhanced secretion of TNF-α and IL-10. Chloroquine may interfere with NETs internalisation by lupus macrophages [77].

Macrophages show intrinsic defects disrupting tissue and immunological homeostasis. Macrophages from lupus-prone MRL/lpr mice show impaired lysosomal maturation with heightened ROS production and attenuated lysosomal acidification, which diminish the ability of lysosomes to degrade apoptotic debris contained within IgG–immune complexes (IgG-ICs). Diminished degradation of IgG-ICs prolongs the intracellular residency of nuclear self-antigens and results in the activation of TLRs such as TLR7 and TLR9. Impaired lysosomal maturation also promotes phagosomal membrane permeabilization, allowing dsDNA and IgG to leak into the cytosol and activate cytosolic sensors AIM2 and TRIM21 [78]. The combined activation of TLRs and cytosolic sensors increases cell death through inflammasome formation and contributes to IFN-α secretion, providing a mechanism for the development of SLE (Fig. 1).

1.2.3. Lipid-activated nuclear receptors as targets for modulation of macrophage

After engulfment, increased cellular fatty acids and oxysterols activate several nuclear receptors to promote clearance of ACs by macrophages [79,80]. Lipid-activated nuclear receptors such as PPARγ, LXRs and retinoid receptors, participate in the regulation of reverse cholesterol transport in macrophages and, as a result, prevent atherosclerosis [81]. PPARs and LXRs are regulated by non-esterified fatty acid and cholesterol metabolites, respectively. They play vital roles in lipid homeostasis. Recent research showed that they also regulate the inflammatory response by cooperating with the glucocorticoid receptor to synergistically transrepress distinct subsets of TLR-responsive genes [82].

LXRs take part in the regulation of macrophage cholesterol homeostasis, inflammatory response, phagocytosis, and apoptosis. LXR activation prevents macrophage cholesterol overload by inhibiting cholesterol uptake and increasing cholesterol efflux [83]. In addition, LXR signaling is also important for effective AC clearance by macrophages via induction of the Mer. LXRα/β knockout mice showed defective AC engulfment, led to the development of autoantibodies as well as deposition of ICs, and the resultant glomerulonephritis. Moreover, systemic administration of LXRs agonist ameliorated lupus-like disease in experimental animals [79]. Activation of LXRs has been shown to antagonize inflammatory gene expression downstream of TLR4 signaling, IL-1β-mediated signaling and TNF-α-mediated signaling [82,84].

PPARγ is expressed abundantly in macrophages and it forms a permissive heterodimer with retinoid X receptors (RXRs). Heterodimers containing a permissive partner (such as PPAR/RXR) can be activated by the ligands of either partner [81]. Macrophage-specific deletion of PPARγ or RXRα leads to lupus-like disease in mice with glomerular damage and enhanced production of autoantibodies to nuclear antigens. PPARγ/RXRα heterodimer also participates in the modulation of phagocytosis by regulating a network of genes such as CD36, Mer, Axl, and C1q. All above indicate that PPARγ and RXR signaling in macrophages are important for the efficient phagocytosis and the maintenance of self tolerance [85].

1.3. Abnormalities in macrophage polarization and activation in SLE

1.3.1. Macrophage polarization in SLE

Monocytes are recruited to the tissues and differentiate into macrophages. Macrophages constitute an important part of innate immune system and they are present in nearly every tissue. One important characteristic of macrophages is the high degree of plasticity, which allows their transition between interchangeable functional phenotypes, depending upon the cytokine composition of their microenviroment. Macrophages can be classified as, but not limited to, classically-activated M1 (infiltrating and inflammatory) macrophages and alternatively-activated M2 (tissue-resident and trophic) macrophages. M2 macrophages are further classified as M2a (pro-fibrotic), M2b (immunity regulating), as well as M2c (deactivated, remodeling or anti-inflammatory) macrophages. With the high degree of plasticity, macrophages participate in many biological processes such as tissue repair, immune regulation and inflammation [86].

The process of monocyte-to-macrophage differentiation contributes to SLE pathogenesis, possibly by polarizing macrophages towards classic M1 activation [87] (Fig. 1). Adoptive transplantation of M2, but not M1 macrophages significantly ameliorated SLE disease activity in clodronate- and activated lymphocyte-derived DNA-treated mice [88]. Besides that, dietary supplements and nutritional therapies have been considered as safe therapeutic strategies for SLE patients. Virgin olive oil, particularly its phenol fraction is effective in reducing LPS-mediated inflammation by interfering with the LPS/TLR4 axis. Phenol fraction from virgin olive oil also inhibits the signature of M1 macrophages while favoring the phenotype of M2 macrophages upon polarization of naive human macrophages. Therefore, virgin olive oil and its phenol fraction possess preventive effects on SLE [89].

PPARγ activation induces the differentiation of human monocytes into anti-inflammatory macrophages and modulates the inflammatory immune response [90]. ACs have been shown to induce PPARγ sumoylation, which blocks the clearance of nuclear receptor corepressor from NF-kB sites within proinflammatory promoters in macrophages [91]. Activated PPARγ interferes with the MAPK pathway through impaired phosphorylation of p38 and extracellular signal-regulated kinase1, both of which locate upstream in the signaling cascade mediating NF-kB activation [92]. Pioglitazone, a specific PPARγ agonist, polarizes macrophages towards M2 activation in SLE patients and exhibits anti-inflammatory effects on macrophages [93]. In addition, phenol fraction from virgin olive oil augments the transcriptional activity of PPARγ in human peripheral blood monocytes [89]. Besides that, as a ligand-activated transcription factor, aryl hydrocarbon receptor (AhR) shows diverse effects on immune response. AhR negatively regulates type I IFN signaling and the development of murine

lupus. The AhR agonist indole-3-carbinol polarizes HMDMs to the anti-inflammatory M2 phenotype. Therefore, AhR could be investigated as a promising target of anti-inflammatory therapies for SLE [94].

Dynamic cell blebbing and the release of AC-derived membrane microparticles (AdMPs) is the characteristic of apoptosis and is thought to be the result of cytoskeleton reorganization and contraction [95]. AdMPs function as potential immune modulators and auto-adjuvant in immune responses, and can trigger IFN-α secretion of pDCs [96]. AdMPs contain autoantigens which are potential autoantibody targets in autoimmune diseases [97–99]. HMGB1 has been detected within AdMPs [100,101]. Nucleosomes released from ACs are concentrated on AdMPs and elicit autoimmune response when present in a complex with HMGB1 [102,103]. Macrophages polarize to a more inflammatory M1-like phenotype after stimulation with AdMPs and /or IFN-α [104]. In addition, macrophages from B6.MRL-Fas^{lpr} mice and SLE patients exhibited decreased expression of CD206, a marker for M2 macrophage, and reduced phagocytic activity, both were corrected by mesenchymal stem cells in an IL-6 dependent manner [105]. Furthermore, C1q regulates macrophage polarization to an M2-like phenotype by programming macrophages to an anti-inflammatory and pro-efferocytic phenotype [47,106]. C1q significantly enhanced the expression of M2-driven cytokine such as IL-13, while decreased the expression of the M1-asssociated chemokine CXCL9 in HMDMs [106].

HMGB1 can skew differentiation of M2-like macrophages towards an M1-like phenotype and, whereafter, reduce phagocytosis of ACs [107]. HMGB1 induces proinflammatory M1-like macrophage differentiation whereas C1q collaborates with HMGB1 to induce the differentiation of monocytes into anti-inflammatory M2-like macrophages. C1q, HMGB1, RAGE, and leukocyte-associated Ig-like receptor-1 form a multimolecular complex in lipid rafts to modulate macrophage polarization, depending on relative levels of C1q and HMGB1 [108]. Besides that, TNF-α-induced protein 8-like 2 (TIPE2) has been found to act as an immune negative molecule critical to homeostasis. TIPE2 suppresses inflammation by inhibiting iNOS activity and NO production. It alleviates experimental SLE through induction of macrophage polarization to an M2 phenotype [109].

Anti-C1q induced a proinflammatory phenotype of HMDMs by increasing LPS-induced production of IL-1β, IL-6, and TNF-a via an FcgRII-dependent pathway, so reversed the C1q-dependent suppression of macrophage mediated inflammation. Investigation on surface markers showed that the combination of anti-C1q and TLR4 stimulation by LPS induced a more M1-like phenotype in HMDMs, compared with an M2-like phenotype elicited by C1q [54].

1.3.2. TLRs signaling and macrophage activation in SLE

Response of nucleic acid sensors induces the generation of type I IFN, pro-inflammatory cytokines, and functions as initial triggers of autoimmunity [110]. Among these, TLR7 is required for the induction of antibodies to RNA and RNA associated proteins, whereas TLR9 activation promotes production of antibodies to dsDNA and chromatin. Co-ligation of BCR and TLRs induces autoreactive B cell proliferation and plasmablast differentiation, which accounts for the production of ANAs in autoimmunity [111]. Dysregulated activation of TLR7 has been linked to the pathogenesis of SLE in humans and mice. Except for its role in the recognition of nucleic acids, TLR7 is also involved in the induction of autophagy and the formation of NETs [112,113].

Members of the triggering receptor expressed on myeloid cells (TREM) family of receptors have been shown to modulate innate immune responses by amplifying or dampening TLR-induced signals. A genome-scale RNA-mediated interference (RNAi)-based screen of mouse macrophages identified TREM-like 4 (TREML4) as a positive regulator of TLR signaling. TREML4 amplifies TLR7-induced signaling and type I IFN responses by recruiting TLR7 and the adaptor myeloid differentiation factor 88 (MyD88) to the endolysosomal compartment, followed by activation of the MAPK p38 as well as phosphorylation of the transcription factor STAT1. Macrophages from TREML4−/− mice are hyporesponsive to TLR7 agonists and failed to produce type I IFN [114] (Fig. 1). TREML4 has been demonstrated to bind to late apoptotic and necrotic cells [115]. Its ligand is still unknown up to now. TREML4 contributes to TLR7 responses probably by acting as a chaperone [116]. Integrative DNA, RNA, and protein evidence also linked TREML4 to coronary artery calcification, a clinical predictor of atherosclerotic coronary artery disease. TREML4 co-localizes with inflammatory macrophages in foam cell regions of the coronary plaque complicated by calcification [117].

Park SH et al. showed that the proinflammatory cytokines TNF and type I IFN induced transcriptional cascades that altered chromatin states to broadly reprogram responses induced by TLR4. TLR4 signaling is almost completely abolished in macrophages pretreated with TNF, whereas type I interferons potentiate the inflammatory function of TNF by priming chromatin to prevent the silencing of target genes of the transcription factor NF-κB and enable robust transcriptional responses to weak upstream signals. Whether type I interferons promote the pathogenesis of SLE in part by preventing the tolerization of genes encoding inflammatory molecules remains to be determined [118]. Antimalarial drugs such as chloroquine and hydroxy chloroquine have been used in the therapy of SLE for a long time. They bind to nucleic acids directly and the interactions between antimalarials and nucleic acids cause structural modifications of the nucleic acids preventing their binding to TLRs, and consequently the suppression of endosomal TLR activation. Furthermore, the antimalarials do not inhibit endosomal proteolysis or increase the endosomal pH [119].

Integrin CD11b combines with the β2 chain (ITGB2, CD18) to form Mac-1, an integrin heterodimer participating in inflammation-induced leukocyte tissue recruitment. Besides that, CD11b also plays vital roles in maintenance of autoreactive B cell tolerance [120]. It negatively regulates innate immune cell activation downstream of TLR pathways [121]. CD11b activation reduces TLR-dependent proinflammatory signaling in macrophages and suppresses type I IFN signaling via an AKT/FOXO3/IRF3/7 pathway [122]. CD11b activation directly inhibits the MyD88 and Toll-interleukin-1 receptor domain-containing adaptor-inducing interferon-beta (TRIF) pathways through promoting degradation of these adaptors via Cbl-b [123].

1.3.3. Inflammasome activation of macrophage in SLE

As a family of multimolecular complexes, inflammasomes are mainly expressed in the cytoplasm of monocytes/macrophages. NLRP3 inflammasome is regarded as one of the most studied members and NLRP3 inflammasome activation has been implicated in the pathogenesis of SLE [124,125]. Activation of caspase-1, the central enzyme of the inflammasome, results in release of active IL-1β and IL-18. As the hallmark antibodies of SLE, anti-dsDNA antibodies are presented in the blood of patients with SLE even before disease onset. Anti-dsDNA antibodies activate TLR4-NF-κB and NLRP3 inflammasome signal pathway in monocytes/macrophages in SLE patients, which depend on the binding to TLR4 and the production of mitochondrial ROS [126]. Both NETs and LL-37 activate caspase-1, in human and murine macrophages (Fig. 1). Moreover, inflammasome activation mediated by NETs and LL-37 is potentiated in macrophages derived from lupus patients. Enhanced formation of NETs in lupus patients further increases inflammasome activation in adjacent macrophages, resulting in a feed-forward inflammatory loop that could potentially lead to disease flares [127].

Beneficial effects of TLR7, TLR8, and TLR9 inhibition in NZBW/F1 Murine lupus model could be, at least in part, due to the blockage of NLRP3 upregulation [128]. In a recent study, caspase-1$^{-/-}$ mice were shown to be resistant to developing lupus and protected from renal IC deposition and kidney damage [129]. Blockade of HMGB1 signaling has also shown success in abrogating caspase-1 activation and LN in BXSB mice [130]. In addition, C1q increases the expression of potent immunoregulatory and immunosuppressive cytokines and down-regulates NLRP3 inflammasome activation in LPS-stimulated HMDMs [106].

DNASE1L3 also participates in the regulation of inflammasome activation by promoting apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) nuclear export and speck formation. DNASE1L3 inhibition blocks inflammasome mediated release of HMGB1 and IL-1β [131].

1.3.4. Autophagy machinery of macrophage in SLE

Autophagy can be induced by LPS through a TRIF-dependent, MyD88-independent TLR4 signaling pathway in macrophages [132]. Research from B. Li et al. showed that aberrant activated autophagy in macrophages contributed to the pathogenesis of murine lupus via promoting proinflammatory cytokine production of TNF-α and IL-6. Therefore, inhibition of autophagy represents a novel regulation strategy for excessive activation of proinflammatory macrophages as well as a new therapeutic target for SLE [133]. On the other hand, Martinez J. et al. found the engagement of noncanonical autophagy, also referred as LC3-associated phagocytosis (LAP), during uptake of apoptotic, necrotic cells by macrophages. LAP facilitates phagosome maturation and subsequent degradation of engulfed cargo, a process dependent on some members of the canonical autophagy pathway, such as Beclin1, ATG5, and ATG7 [134]. Macrophages defective for LAP fail to digest phagocytosed contents efficiently and result in increased secretion of proinflammatory cytokines and decreased secretion of anti-inflammatory cytokines [135] (Fig. 1). Moreover, LAP-deficient mice show SLE-like disease and repeated injection of dying cells into LAP-deficient mice may accelerate this process [134]. In addition, genome-wide association studies have identified polymorphisms both in *Atg5* and *Atg7* as markers of predisposition for SLE [136,137].

2. Macrophages in affected organs of SLE

SLE is characterized by multi-organ damage with a variety of clinical manifestations. We just discuss the role of macrophages in LN, skin and liver lesion, and cardiovascular disease here.

2.1. Macrophages in LN

About 40–75% SLE patients show symptoms of renal disease [138]. Macrophages contribute to LN through the release of multiple inflammatory mediators including RANTES, IP-10, VCAM-1, iNOS, MMP-9 and HMGB1. MMP-9 participates in LN pathogenesis by contributing to extracellular matrix damage and podocyte injury. HMGB1 stimulates macrophage to release proinflammatory cytokines, including MCP-1, which can attract more macrophages into kidney, thereby forming a positive feedback loop that amplifies disease [139]. Colony stimulating factor-1 (CSF-1) is required for macrophage survival, proliferation and activation. Its expression is enhanced in the tubular epithelial cells (TECs) during kidney inflammation. In lupus-susceptible mice, ischemia-reperfusion (I/R) injury induces CSF-1 in injured TECs and stimulates the expansion of M1 macrophages. Then overactive M1 macrophages mediate defective renal repair, leading to early-onset LN. In lupus-resistant mice, however, increasing CSF-1 hastens renal healing after I/R by shifting M1 “destroyer” macrophages toward the M2 “healer” phenotype [140]. A selective inhibitor of the CSF-1 receptor kinase, GW2580, was used for macrophage depletion and ameliorated nephritis induced by pathogenic antibodies. Macrophage depletion significantly decreases the expression of cytokines contributing to disease pathogenesis in kidney. GW2580 also inhibits the recruitment of inflammatory monocytes from the circulation, so to minimize kidney macrophage infiltration, by negatively affecting proliferation and survival of tissue resident macrophages [139].

2.2. Macrophages in skin and liver injuries of SLE

Skin is the second most affected organ (after the kidney) in patients with SLE [141]. MRL/lpr mice also exhibit spontaneously lupus-like disease with skin involvement [142,143]. Ultraviolet light exposure may induce aberrant keratinocyte apoptosis in the skin of lupus patients, whereas the defective phagocytosis function of macrophage results in the release of autoantigens, which further stimulates the immune system [144]. Some autoantibodies, such as anti-Ro and anti-galectin 3 antibodies, have been linked to the skin damage in SLE [145,146]. Skin deposited IgG triggers skin damage by binding to apoptotic keratinocytes and promoting skin inflammation [147,148]. Deficiency of macrophage dramatically ameliorates skin illness in MRL/lpr mice, indicating the essential role of macrophage in the process [149]. In addition, TNF-α and IL-1, both mainly produced by monocytes/macrophages, participate in skin disease induced by deposited IgG [150–152]. Besides that, spleen tyrosine kinase (Syk) is involved in many signaling pathways in various cells, including macrophages [153]. Syk inhibitor may prevent the development of skin and kidney disease, ameliorate established tissue injuries in lupus-prone mice [154]. Similar to skin lesion, hepatic deposition of lupus IgG has been confirmed as an important pathological factor for SLE-associated liver injury. IgG deposition in the liver of patients with SLE leads to the activation of Kupffer cells and facilitates the production of proinflammatory cytokines including TNF-α. Lupus-IgG-stimulation triggers apoptosis of hepatocytes around the inflamed sites in the liver. Macrophage-depleted mice show ameliorated liver lesions induced by lupus IgG. Both macrophage and TNF-α participate in the development of lupus-IgG-induced hepatic inflammation. Moreover, hepatic inflammation is also regulated by the Syk signaling pathway and blocking IgG signaling by a Syk inhibitor may suppress the liver damage in SLE [155].

2.3. Macrophages in cardiovascular disease of SLE

Atherosclerotic cardiovascular disease (CVD) risk is significantly increased in patients with SLE [156]. An early feature of the atherosclerotic lesion is infiltration with inflammatory cells, especially monocytes/macrophages. Monocytes and macrophages within the vascular subendothelial space play key roles in atherogenesis [157]. When macrophages ingest ACs, they acquire the lipids, carbohydrates, protein, and nucleotides from the ACs, which pose a significant metabolic burden on the macrophages [158]. The regulation of lipid metabolism in macrophages with internalized ACs is closely related to the maintenance of cell-autonomous homeostasis as well as the development of atherosclerosis. Macrophages which internalize large amounts of cholesteryl fatty acids (foam cells) accumulate along with necrotic cells arising from the impaired clearance of apoptotic cells, subsequently followed by the activation of pro-coagulant and pro-thrombotic pathways as well as the development of atherosclerosis [159]. The presence of monocytes/macrophages in mature plaque elevates the risk of plaque rupture and thrombosis [160].

Macrophages express scavenger receptors (SR), such as lectin-like oxidised low-density lipoprotein receptor 1 (LOX1R), CD36, SR-AI/II and SR-BI, all of which mediate internalization of lipoproteins [161]. SR-A messenger RNA was significantly increased in PBMCs from SLE patients relative to normal subjects, and positively correlated with IFN-inducible genes expression. IFN-α priming enhances lipid uptake and foam cell formation by up-regulating the expression of SR-A in human monocyte/macrophages. Therefore, activation of the IFN signaling pathway may be associated with the risk of atherosclerosis by affecting plaque formation in patients with SLE [162].

HDL suppresses a subset of genes that regulate the response to type I IFN in LPS-stimulated macrophages independent of sterol metabolism [163]. Unmodified, healthy HDL blocks TLR-induced proinflammatory cytokine production via inducing the expression of activating transcription factor 3 (ATF3) [164]. On the other hand, oxidized, dysfunctional HDL loses its cardioprotective effects and has been linked to SLE-related CVD. NETs in lupus may promote proatherogenic modifications in HDL and the oxidized lupus HDL exhibits impaired

cholesterol efflux capacity [165]. Lupus HDL potentiates proinflammatory responses in macrophages via NF-κB activation and decreased ATF3 activity, depending on LOX1R and ROCK1/2 [161].

3. Conclusion

The pathogenesis of SLE is incompletely understood. Macrophages have recently been shown to play essential roles in the pathogenesis of SLE. Defects in the phagocytosis of ACs by macrophages lead to release of self-antigens and initiation of autoimmunity. Moreover, aberrant inflammatory macrophage activation and polarization also potentiate inflammation and tissue injuries in SLE. Both environmental factors and intrinsic mechanisms contribute to the functional regulation of macrophages. Some molecules may modulate the function of macrophages at multiple levels, via different signaling pathways. Among these, C1q may function as opsonizing protein and bridge molecule, and could enhance the expression of some proteins related to engulfment of ACs. Meanwhile, C1q also regulates macrophage recruitment, the proinflammatory signaling and polarization of macrophages. Of note, newly-identified physiological role of EPO signaling in promoting dying cell clearance further deepens our understanding about immune homeostasis. Besides that, dietary supplement such as virgin olive oil possesses preventive effects on SLE by inhibiting TLR4 signaling and favoring M2 polarization of macrophages. In the future, development of more effective and safer therapies must be based on the elucidation of SLE pathogenesis, among which the role of macrophages constitutes an important part.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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