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Rheumatoid arthritis and systemic lupus erythematosus: Pathophysiological mechanisms related to innate immune system

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Abstract

Rheumatoid arthritis and systemic lupus erythematosus are two highly prevalent autoimmune diseases that generate disability and low quality of life. The innate immune system, a long-forgotten issue in autoimmune diseases, is becoming increasingly important and represents a new focus for the treatment of these entities. This review highlights the role that innate immune system plays in the pathophysiology of rheumatoid arthritis and systemic lupus erythematosus. The role of the innate immune system in rheumatoid arthritis and systemic lupus erythematosus pathophysiology is not only important in early stages but is essential to maintain the immune response and to allow disease progression. In rheumatoid arthritis, genetic and environmental factors are involved in the initial stimulation of the innate immune response in which macrophages are the main participants, as well as fibroblast-like synoviocytes. In systemic lupus erythematosus, all the cells contribute to the inflammatory response, but the complement system is the major effector of the inflammatory process. Detecting alterations in the normal function of these cells, besides its contribution to the understanding of the pathophysiology of autoimmune diseases, could help to establish new treatment strategies for these diseases.

Keywords

Rheumatology, clinical immunology, rheumatoid arthritis, systemic lupus erythematosus, innate immunity

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Introduction

The innate immune system is the first line of defense for the organism, especially protecting it against infectious agents. It is composed of physical barriers, humoral molecules, and different immune cells that are responsible for inducing the initial inflammatory response. Although it does not have the specificity of the adaptive immunity, it can recognize several molecular patterns present in different pathogens or injured tissues, to activate the inflammatory cascade. The innate immune system plays a critical role in the activation of the adaptive immune response. However, the role of the innate immune system in the development of autoimmunity has not been studied enough.[1]

Systemic lupus erythematosus (SLE) is an autoimmune disease with important chronicity features, which affects multiple organ systems, and whose evolution is characterized by the appearance of remissions and recurrences. Its etiology is still unknown; however, it is known that there is an interplay between genetic, environmental, hormonal, and immunological factors. Rheumatoid arthritis (RA) is a multisystem inflammatory disease, which mainly affects the joints and can lead to deformities and functional limitation without appropriate treatment, with high rates of disability and reduced survival of people who suffer from it. It is characterized by

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inflammation, synovial hyperplasia, autoantibody production (rheumatoid factor (RF), anti-citrullinated protein), destruction of cartilage, bone deformities, and systemic involvement of cardiovascular, pulmonary, neurological, and endocrine systems.[2,3]

The pathophysiology of both diseases is related in genetic, environmental, and immunological aspects. This review will consider the immune mechanisms of these diseases, emphasizing in the innate immune system. Both disorders share an autoimmune etiology but they are different in their immunological mechanisms, which determine the different manifestations and implications.

Methodology

The aim of this review was to present the latest evidence regarding the role of innate immune system components in the pathophysiology of RA and SLE. A literature review was developed by searching the evidence available in English language regarding the role of innate immunity in RA and SLE. The search was made using MEDLINE PubMed database, with Mesh Terms. The first search used the terms: "Arthritis, Rheumatoid"[Mesh] AND "Immunity, Innate"[Majr]. The second search used the terms: "Lupus Erythematosus, Systemic"[Mesh] AND "Immunity, Innate"[Majr]. No exclusion criteria were applied regarding the type of study or publication year.

The search was developed by two different researchers who applied the same terms and strategies to find the studies. The initial selection of studies was made based on the title, and then, the selected papers were assessed by reading their abstracts. Finally, selected studies were assessed through detailed reading in order to select the final studies to be included. A total of 195 papers were included in this review.

Pathophysiological factors

Genetic factors

Immunogenetics has major implications in the development of autoimmune diseases. In SLE, genetic concordance in monozygotic twins has been found to be 24%–56% compared to 2%–5% in dizygotic twins.[3] The heritability index (tool to quantify the genetic influence, regardless of the prevalence of the disease) found for SLE ranges between 43% and 66% according to different population studies, with a hazard ratio of recurrence among siblings of patients with SLE up to 29 times higher than in general population.[4] In RA, monozygotic twin concordance is 15.4%, and dizygotic twins had 3.6% in a cohort study of English patients with RA,[5] although another study found that heritability index is about 60%.[6] In particular, there are other genetic important factors involving the human leukocyte antigen (HLA) and non-HLA genes.

Regarding HLA, it has been studied in all autoimmune diseases, but in RA, it is especially important as it constitutes the main genetic risk factor. In Table 1, some of the main genetic factors related to RA and SLE are summarized.

The first discovery on this aspect was the presence of a greater incidence of *HLA-DR4* genotype, found in 70% of patients with RA and in 28% of healthy controls.[7] Gregersen later described the "shared epitope" hypothesis, which is about the existence of a specific amino acid sequence (QKRAA, QRRAA, RRRAA) in the 70–74 position located in the third hypervariable region of the DR Beta1 chain that predisposes to antigen presentation of certain peptides. This sequence can be found in alleles *HLA-DRB1*04* and *HLA-DRB1*01*. This suggests that alterations in the repertoire of T cells, antigen presentation, and affinity for certain peptides could promote autoimmune processes.[8] Recently, the nomenclature system for the shared epitope has changed, as it is now based on the amino acids at positions 70 and 71. Based on this system, five groups were identified: S1, S2, S3P, S3D, and X. Evidence shows that the S2 and S3P groups are the ones associated with a higher risk of developing RA.[9] Despite these findings, it is said that the genetic contribution of shared epitope is only 30%, becoming a factor "neither necessary nor sufficient" for the development of RA.[10] Furthermore, the association of the "shared epitope" with the disease varies according to ethnic groups; for example, in Latin American population, the presence of the *HLA-DRB1* allele, especially the 0404 variant, has been identified as a major risk factor for the development of the disease.[11,12] It is also important to clarify that the "shared epitope" is found only in patients with positive anti-citrullinated peptide antibody (ACPA), which also leaves out ACPA-negative patients. However, it is fully recognized that the presence of alleles that carry the "shared epitope" constitutes a risk factor for disease severity.[13]

Considering associations between SLE and HLA genes, the most important is related to chromosome 6, specifically 6p21.3, which encodes for a large number of genes associated with the immune system.[14] Subsequent studies have established associations between genetic variants of genes related to HLA II in different human populations. In European and Asian populations, *HLA-DR2* and *HLA-DR3* (*DRB1*1501* and *DRB*0301*, respectively) have been associated with SLE.[15,16] A study from 2012 in Colombian population describes the association of *HLA-DRB1*1501* and *HLA-DRB1*0301* with the development of lupus. Also *HLA-DRB1*0701* and *HLA-DRB1*0802* are associated with the development of lupus nephritis (LN).[17] Correlation has been established between related genes encoding HLA class III, complement factors, and susceptibility to develop SLE.[18,19] Protective factors have also been found such as the role of *HLA-DRB1*13*, which is thought to confer protection, especially against the development of SLE. It seems that this allele induces a more effective antigen presentation and increases the efficiency of clonal deletion of autoreactive lymphocytes. Complete deficiencies of C2 and C4 are rare but have been associated with a high risk of developing SLE.[20]

Table 1. Main genetic factors associated with RA or SLE.

Gene	Function	RA	SLE
HLA			
HLA-DRw4	Antigen presentation	X	
*HLA-DRB1*04*	Antigen presentation	X	
*HLA-DRB1*01*	Antigen presentation	X	
*HLA-DRB1*1501*	Antigen presentation		X
*HLADRB*0301*	Antigen presentation		X
No HLA			
PADI4	Conversion of arginine to citrulline	X	
PTPN22	Several signaling pathways synthesis	X	X
CTLA4	Inhibitory signal to T cells	X	
TRAF1C5	Bind several protein kinases	X	
STAT4	Signaling	X	X
IRF5	IFN production and regulation		X
FcγR	Phagocytosis		X
ITGAM	Phagocytosis		X
TNFSF4	Increase TL survival		X
BLK	Protector role in both diseases.	X	X
CD44	Protector role in both diseases.	X	X

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; TL: T lymphocyte; *PADI4*: peptidylarginine deiminases citrullinating enzyme; *PTPN22*: protein tyrosine phosphatase non-receptor type 22; *CTLA4*: cytotoxic T lymphocyte–associated protein 4; *TRAF1C5*: tumor necrosis factor receptor-associated factor 1 complement component 5; *STAT4*: signal transducer and activator of transcription 4; *IRF5*: interferon regulatory factor 5; *FcγR*: Fcγ receptors; *ITGAM*: integrin alpha M; *TNFSF4*: tumor necrosis factor (ligand) superfamily member 4; IFN: interferon; *BLK*: B lymphoid tyrosine kinase.

Non-HLA factors have become increasingly important in recent years, with the advent of typing techniques such as genome-wide association studies (GWAS). A large number of non-HLA genes associated with disease susceptibility, severity, and activity have been identified. About 39 single-nucleotide polymorphisms (SNPs) associated with RA have been identified, including the peptidyl arginine deiminase 4 (*PADI4*) enzyme; the protein tyrosine phosphatase non-receptor type 22 (*PTPN22*); cytotoxic T lymphocyte–associated protein 4 (*CTLA4*); tumor necrosis factor receptor–associated factor 1, complement component 5 (*TRAF1C5*); and signal transducer and activator of transcription 4 (*STAT 4*).[21]

Regarding SNPs related to SLE, we can also find interferon (IFN) regulatory factor 5 (*IRF5*), *STAT 4*, *PTPN22*, related genes IgG constant fraction, integrin subunit alpha M (*ITGAM*), and B lymphoid tyrosine kinase (*BLK*) as those related to the complement component C1q.[18] Considering *ITGAM*, it has been reported that the A-allele of *ITGAM* rs1145679 is associated with an increased susceptibility for the development of SLE in European, African, and Hispanic populations.[22]

Other genes described are the ones encoding the tumor necrosis factor (ligand) superfamily, member 4 (*TNFSF4*) and its receptor, IL-10, interleukin-1 receptor-associated kinase 1 (*IRAK1*). The TNF receptor-associated factor 6 (*TRAF6*), which is involved in the activation of NF-kB (nuclear factor-kappa B), has been associated with an increased susceptibility for both RA and SLE development.[22]

A recent meta-analysis, developed by Jeong and colleagues, identified several genes that were confirmed regarding their association with SLE by using GWAS technique. An important amount of genes identified was associated with the interferon signaling pathway that is involved in the breaking of self-tolerance by the activation of antigen-presenting cells as an answer to autoantigens. The genes identified were *IRF5, IRF7, IRF8, PRDM-1-ATG5*, and *TYK2*.[23] These SNPs could be important in the genetic search for new biomarkers that can predict disease behavior or potential targets for new therapies for both SLE and RA.

Epigenetics has gained a relevant role in the pathogenesis of SLE. A recent study published in 2017 demonstrates that genomic DNA in lymphocytes expressed altered methylation patterns, and it was linked to an aberrant activation of the mitogen-activated protein kinase (MAPK). The altered methylation pattern was associated with an increased expression of co-stimulatory molecules as CD-11A, CD-70, and CD-40L, and pro-inflammatory cytokines as IL-17A. Also, an increased expression of growth arrest and DNA-damage-inducible protein 45-alfa (GADD45-alfa) was observed in T cells of patients with SLE. This behavior was associated with an increased DNA demethylation activity. The aberrant functioning of transcription factor networks is also present in patients with SLE. Some molecules, such as cAMP-responsive element modulator alfa (CREM-alfa), are increased in T cells of these patients. This molecule is associated with epigenetic remodeling of genes inducing the increased production of effector T cells in SLE. Another important concept

that has gained relevance is the role of non-coding RNA. These RNA molecules could be involved in the process of DNA methylation. For example, miRNA126 has been linked with a reduction in the activity of DNA methyltransferase 1 (DNMT-1) in T cells of patients with SLE.[24]

Regarding RA, limited evidence is available for epigenetics. However, some data have revealed that a global hypomethylation is present in patients with RA compared to healthy controls. This pattern of hypomethylation is especially observed in the fibroblast-like synoviocytes (FLS), promoting a pro-inflammatory phenotype for these cells. Other studies have shown hypomethylation of IL6 genes in mononuclear cells, increasing the expression and production of this pro-inflammatory cytokine in patients with RA. Also, an increased expression of miRNA-115 and 203 has been observed in patients with RA, a process that is associated with an increased production of matrix metalloproteinase-1 and IL-6, molecules that are critical in the pathophysiology of the disease.[25]

Environmental factors

Environmental factors constitute an important aspect of the pathophysiology, as the combination of genetic and environmental factors is associated with the onset of autoimmune processes.

Smoking is a common risk factor for both diseases, although the association is much clearer and stronger for RA than SLE. A meta-analysis in 2004 found a slight association between current smoking and the development of SLE, but found no association between being exposed to smoking in the past and the development of SLE.[26] It has been found that cigarette smoking is related to specific manifestations in SLE.[27] However, recent evidence shows that in patients with SLE, smoking stimulates the expression of CD95 in the surface of lymphocytes, inducing the loss of tolerance. In addition, the expression of anti-dsDNA is increased in these patients.[28]

In RA, smoking is not only a risk factor for developing the disease[29] but it also induces citrullination (post-transduction modification of arginine residues to citrulline) of proteins, which may lead to the production of ACPA, especially in patients with the presence of the shared epitope sequence.[30]

Regarding alcohol consumption in SLE, there are reports of a protective role. It is based in the fact that alcohol reduces the synthesis of pro-inflammatory cytokines such as TNF, IL-6, IL-8 by monocytes and macrophages (MCs). Also, the presence of antioxidant substances, such as resveratrol and humulone in certain beverages like beer and wine, is associated with a decrease in the production of IFN. Although evidence supports a protective role, more studies are required to clarify this.[28]

Occupational exposures and air pollution have also been associated with the development of SLE. The silica dust exposure is a risk factor, owing to the fact that it acts as immune adjuvant that induces apoptosis and the release of intracellular antigens, an increased production of cytokines, oxidative stress, and reduction of regulatory T cells. In animal models, the exposure to silica was associated with an increased development of glomerulonephritis and proteinuria. Asbestos has also been associated with SLE. It induces the production of antinuclear antibodies. The exposure to high levels of dust has been associated with an increased risk of developing autoimmunity, because it increases pulmonary tissue inflammation, oxidative stress, and epigenetic changes.[31]

Also in RA, the role of occupational exposure and air pollution has been studied. One study showed that women living near highways present an increased risk of developing RA. Also a study made in Taiwan concludes that high levels of nitrogen dioxide (and air pollutant) were associated with an increased risk of RA. Air pollution seems to be a risk factor for the development of the disease; however, more evidence is required. Regarding occupational exposure, the most prominent one is silica, as it has been described in the development of Caplan's syndrome. It also increases the risk to present ACPA-positive RA.[32]

Other environmental risk factors in SLE are viral infections and ultraviolet light (UVL). In a study published in 2008 by Zandman-Goddard et al.,[33] they established an association between neuropsychiatric lupus and rubella antibody titers, although not statistically significant. Furthermore, Epstein–Barr Virus (EBV) infection has been linked to some SLE phenotypes.[34] Similarly, some vaccines have been related to the onset and/or severity of SLE.[35] The role of UVL, natural or artificial, has been extensively studied in recent years and has been established as a factor that triggers the onset of the disease, increases skin lesions, and alters some immune system functions such as cleaning of apoptotic bodies and functions related to vitamin D.[36,37] Other factors such as hormones, specifically exogenous estrogens, have more controversial associations, so their specific role in SLE has not been elucidated.[34] Drugs such as procainamide and hydralazine inhibit normal DNA methylation, altering its interaction with transcription factors and therefore the expression of different genes, so they are capable of inducing symptoms similar to SLE in healthy individuals.[38]

There are other interesting environmental factors associated with RA. Periodontitis is a potential risk factor due to the presence of the peptidyl arginine deiminase (PAD) enzyme in *Porphyromona gingivalis*. They are present in 80%–90% of patients with periodontitis, which may citrullinate proteins differently to the PAD present in humans, leading to the creation of new arthritogenic antigens.[39] Gastrointestinal bacteria are also related to RA, as they might trigger autoimmune processes in patients with predisposing factors.[40] Other risk factors described include female gender, age, obesity (especially for ACPA-negative RA), among others.

Table 2. Role of innate immune system and its cells in RA and SLE.

Component	Normal function	Role in RA	Role in SLE
MC	- Phagocytosis and clearance of apoptotic bodies and cellular debris. - Production of cytokines. - APC.	- Overactivation through PAMP and DAMP. - Overproduction of TNF-alpha. - Increased number of MC in ECM.	- Decreased phagocytic function and clearance of apoptotic bodies and cellular debris. - Increased infiltration and proliferation in renal tissue. - Decreased synthesis of IL-10 and increased IL-12.
NKC	- Cytotoxic function. - IFN production.	- Antibodies production control. - Decreased cytotoxic activity.	- Decreased cytotoxic activity. - Increased NKC apoptosis. - Increased IFN-γ production.
NT	- Early response to infection. - Phagocytic function. - ROS and proteolytic enzymes liberation.	- Increased ROS and proteolytic enzymes liberation in joint. - Increased VEGF secretion.	- Increased NET liberation. - Increased ROS liberation. - Increased cytokine production (TNF-alpha, IFN-γ, IL-8).
DC	- Phagocytosis and clearance of apoptotic bodies and cellular debris. - Professional APC. - Immune response amplification.	- Present the arthritogenic antigens. - Overactivation through DAMP. - Increased number in joints. - Possible anti-inflammatory function.	- Decreased phagocytic function. - Increased IFN-alpha production by pCD. - APC function increased. - Accelerated mCD differentiation and maturation. - Possible regulatory function.
CS	- Opsonization of microorganism, apoptotic bodies, and cellular debris. - Cytotoxic function. - Cellular chemotaxis. - Early response to infection.	- Overactivation with decreased levels in joints. - Possible role in rheumatoid vasculitis.	- Protector role in the disease. - Decreased activation of three complement ways. - Decreased phagocytosis induction. - Increased production of antibodies against its components.
FLS	- Synthesis of ECM and synovial liquid components.	- Synthesis of ECM-degrading molecules. - Recruits leukocytes from peripheral blood.	- None.
OC	- Bone resorption.	- Overactivation which leads to bone erosions. - Uncontrolled activity of OC.	- Decreased osteoclastogenesis.

RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; MC: macrophage; APC: antigen-presenting cell; PAMP: pathogen-associated molecular patterns; DAMP: damage-associated molecular pattern; TNF-alpha: tumor necrosis factor alpha; ECM: extracellular matrix; IL-10: interleukin 10; IL-12: interleukin 12; IFN-alpha: interferon-alpha; NKC: natural killer cell; IFN-γ: interferon-gamma; NT: neutrophil; ROS: reactive oxygen species; VEGF: vascular endothelial growth factor; NET: neutrophil extracellular trap; IL-8: interleukin 8; DC: dendritic cell; pCD: plasmacytoid dendritic cell; mCD: myelocytic dendritic cell; FLS: fibroblast-like synoviocytes; CS: complement system; OC: osteoclast.

Immune response

Almost all cells belonging to the immune system are involved in the pathogenesis of RA and SLE. More attention has been paid to the adaptive responses, but recently, the role of the innate immune system has been reconsidered and its role in the development of inflammation in autoimmune diseases has been recognized, leading to a better understanding of the pathophysiology. Thus, alterations of normal function of complement system (CS), and innate immune cells (MCs, natural killer cells (NKCs), dendritic cells (DCs), neutrophils (NTs)) contribute to the development of autoimmunity. The alterations of normal functions of innate immune cells are summarized in Table 2. These alterations by themselves may not be enough to trigger the autoimmune process but they are key players in their development (Figures 1 and 2).

Rheumatoid Arthritis

Macrophages

Monocytes/MCs are cells derived from hematopoietic myeloid precursors, and when they are stimulated by the monocyte colony-stimulating factor (M-CSF) and the granulocyte-monocyte colony-stimulating factor (GM-CSF) in the presence of interleukin 13, they differentiate into mature monocytes to enter the bloodstream.[41] Inflammatory stimuli, due to interactions between selectins, B2 integrins, and chemokines (and its CCR9 receptor[42]) and CD31, mediate monocyte adherence to activated endothelium.[43] These cells become tissue MCs when they leave the bloodstream and have the ability to polarize between M1 and M2. Classical pathway (CP) (mediated by IFN-γ and TNF-alpha) leads to M1 MC and alternative activation (mediated by IL-4 and IL-13 in the case of M2a, by

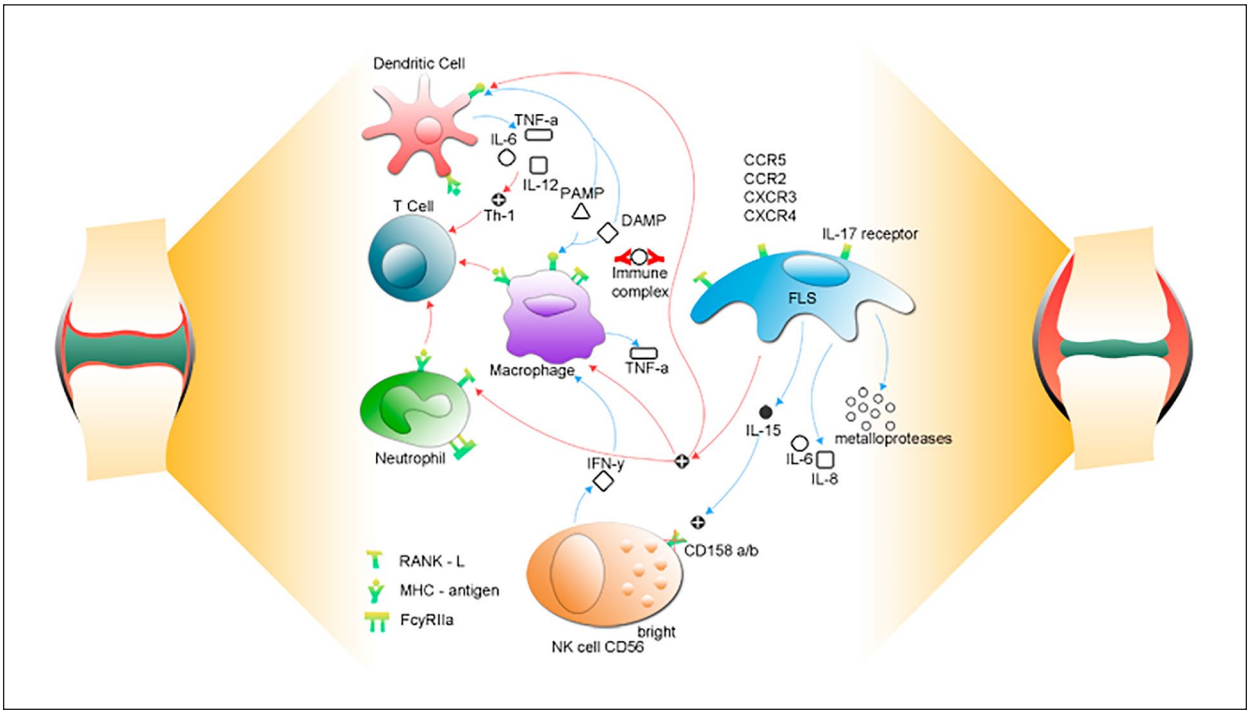

Figure 1. Innate immunity interactions present in rheumatoid arthritis. FLS are increased in number and produce molecules that broke down the extracellular matrix, such as the metalloproteinases, and they also have increased expression of chemokine receptors (CCRs and CXCRs) in the surface, inducing more proliferation of FLS. FLS produce pro-inflammatory cytokines that stimulate infiltrating cells present in joints such as NK cell, neutrophils, macrophages and dendritic cells, which also increase the production of pro-inflammatory cytokines, aside from the stimulation developed by the presence of immune complexes, PAMPs and DAMPs. The whole complex interaction of the different cells and pro-inflammatory molecules contributes to the chronic inflammation that characterizes this pathology.

FLS: fibroblast-like synoviocytes; NK cell: natural killer cell; PAMP: pathogen-associated molecular patterns; DAMP: damage-associated molecular pattern; TNF-a: tumor necrosis factor alpha; MHC: major histocompatibility complex; Th1: T helper cell type 1; IL-6: interleukin 6; IL-8: interleukin 8; IL-12: interleukin 12; IL-15: interleukin 15; IL-17: interleukin 17; IFN-γ: interferon-gamma; CCR5: CC chemokine receptor type 5; CCR2: CC chemokine receptor type 2; CXCR3: CXC chemokine receptor type 3; CXCR4: CXC chemokine receptor type 4; a/b: antibody; RANK-L: receptor activator of nuclear factor kappa-B ligand; FcRIIa: human immunoglobulin receptor IIa.

immune complexes (ICs) and Toll-like receptor (TLR) agonists in the case of M2B, and IL-10 and glucocorticoids in the case of M2c) leads to M2 MC.[44] Depending on the way in which MCs are activated, they will have different functions; M1 effector mechanisms are responsible for bactericidal actions against intracellular parasites; lysis of tumor cells; significant cytokine production such as IL-1, IL-6, IL-12, TNF-alpha; production of free radicals and nitric oxide; and increased expression of molecules of the major histocompatibility complex type II, CD86, leading to facilitate the presentation of antigens to Th1. In contrast, the M2 plays an important role in tissue remodeling and immune regulation.[45]

Activated MCs express the receptor for the Fc portion of IgG (FcγR) that interacts with Immune complexes (ICs), and TLRs that interact with pathogen-associated molecular patterns (PAMPs) (exogenous molecules) and damage-associated molecular patterns (DAMPs) (endogenous molecules).[43] This is crucial in the pathophysiology of autoimmune diseases, because MCs can be activated due to strange antigens coming from infectious microorganisms (PAMPs pathway) or due to self-antigens coming from damaged tissue or cellular stress (DAMPs pathway), leading to the onset of inflammatory response.

MCs are considered the most important cells in RA because they are the principal TNF-alpha producers, and this cytokine is fundamental in RA pathogenesis.

The most important DAMPs involved in RA immune response are proteoglycan derivatives like hyaluronate, fibronectin fragments, heat shock proteins, HMGB-1 (high mobility group box-1). TLR signaling is mediated by *MYD88* (myeloid differentiation primary response gene 88) that activates MAPK (mitogen-activated protein kinases) and NF-kB, leading to the transcription of inflammatory mediators like TNF-alpha. Besides that, TLR3 (the only one that does not go through the MyD88 pathway) and TLR4 can function through interferon regulating factors (IRFs).[46]

Cytokines also play an important role in the innate immune response in RA, either as an activator or as a product of cellular activation. It is known that the number of MCs increases in the synovial fluid of patients with RA,[47] and

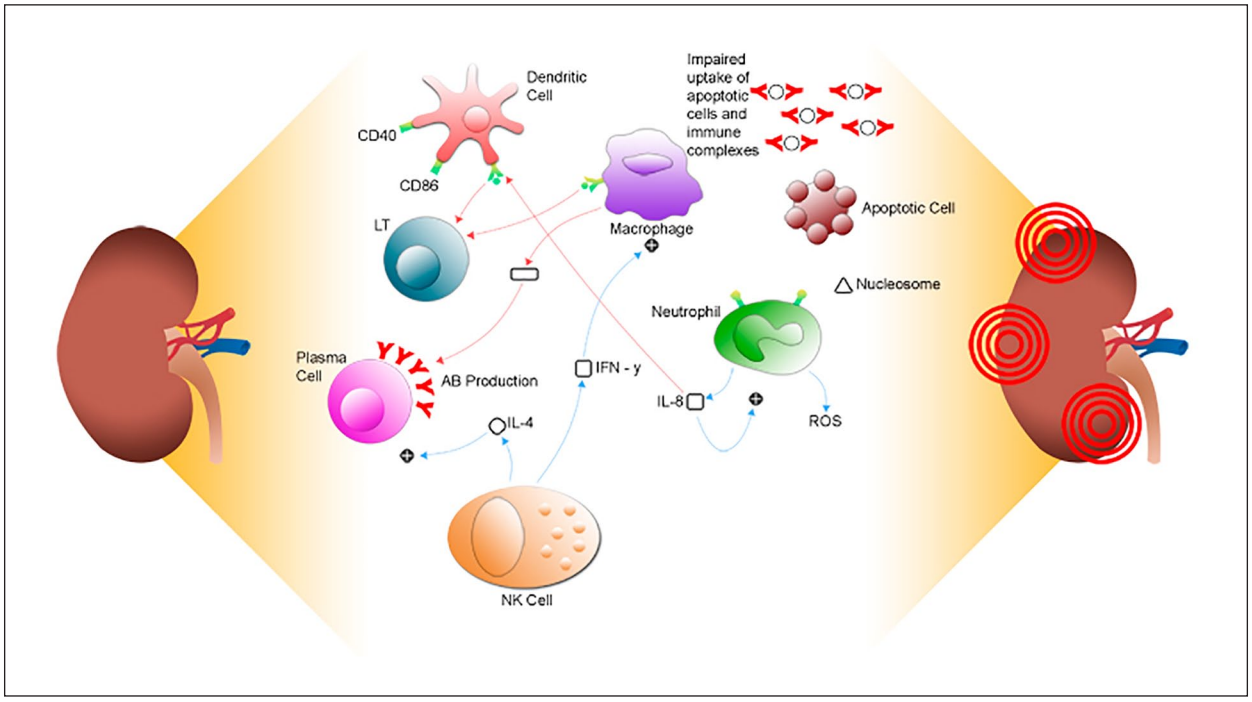

Figure 2. Innate immunity interactions present in systemic lupus erythematosus. Macrophages present an impaired ability for phagocytosis of apoptotic bodies and clearance of immune complexes. These immune complexes that are not degraded accumulate in different organs (such as kidneys), in which they induce tissue damage and increase the production of apoptotic bodies. Accumulation of apoptotic cells increases the presence of self-antigens that bind to follicular dendritic cells at the lymph nodes, increasing probability of antigen presentation to autoreactive lymphocytes, especially B-lymphocytes, inducing the loss of tolerance, and production of autoantibodies. Also, NK cells in patients with SLE produce higher levels of IL-4, and IFN-γ, which is associated with increased cytotoxicity. Neutrophils are also involved, as they induce the loss of peripheral self-tolerance through self-activation of Toll-like receptors by nucleosomes phagocytosed by these cells, inducing the production of IL-8 and recruitment of antigen-presenting cells. Also, neutrophils are constantly producing ROS in these patients.
IFN-γ: interferon-gamma; LT: T lymphocyte; ROS: reactive oxygen species; NK cell: natural killer cell; IL-4: interleukin 4; IL-8: interleukin 8.

they appear early in the disease and are related to joint destruction.[48] The increased number of MCs in the synovial fluid is due to several reasons: increased chemotaxis, decreased lymph drainage,[49] and reduction in apoptotic processes in these cells due to decreased expression of B-cell lymphoma 2 (Bcl-2) pro-apoptotic proteins.[50] It has been described recently an overexpression of sirtuin-1 (SIRT-1), a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase, is responsible for the regulation of transcription factors such as p53, DNA repair factor Ku70, NF-kB, and p53 transcriptional coactivator. This enzyme inhibits apoptosis by deacetylation of Ky70 factor or by protecting epithelial cells from p53-mediated apoptosis.[51] SIRT-1 expression is stimulated by TNF-alpha and it is increased in RA patient's synovial fibroblasts and monocytes. This way promotes pro-inflammatory cytokine production and inhibits inflammatory cell apoptosis.[52]

Both peripheral blood monocytes and synovial MCs are stimulated to produce these cytokines through its interaction with ICs containing ACPA. Recently, in a study using citrullinated fibrinogen ICs, it was found that this process is mediated by the interaction of TLR-4—Myd88 and FcyR.[53]

In addition to TNF-alpha, there are other important cytokines related to MCs like IL-1, macrophage migration inhibitory factor (MIF) (which is able to activate and recruit MCs), IL-6, IL-10, IL-12, IL-15, IL-18, IL-17 (its receptor is present on MC membrane), and receptor activator nuclear factor-kappa B (RANK)/receptor activator nuclear factor-kappa B ligand (RANKL)/osteoprotegerin.[41]

MCs also play an important role in the development of atherosclerosis, and considering that the main cause of mortality in patients with RA and SLE is cardiovascular disease, it takes even greater importance. Their increase in activation could actually contribute to this high incidence of cardiovascular disorders.[54]

Polarization of MCs to M1 or M2 subtypes also appears to be important in RA. It has not been widely studied, although it is known that patients with RA and peripheral spondyloarthropathies (SpA) contain similar numbers of synovial MCs. However, their immune phenotype changes according to the disease: the M1 and its cytokine profile (IFN-γ, TNF-alpha) are most predominant in RA joint, whereas in SpA, M2 and their cytokine profile (IL-4, IL-10, IL-13) are more frequent.[55]

Recently, one study investigated the differences in the polarization into MCs from patients with RA and osteoarthritis (OA), finding that OA patients have more number of M2 type MCs than RA patients, whose type tends to be more M1-type.[56] This reinforces the pro-inflammatory role of MCs in RA, which is different from a non-inflammatory disease like OA. This is why it has been suggested that the decrease in the number of MCs may be a therapeutic target.[57]

The activation of the Notch signaling pathway is essential in the pathogenesis of the disease, as it has been observed that synovial tissue in patients with RA increases the activation of Notch, which is an important inductor of macrophage polarization toward M1 subtype. This favors the production of pro-inflammatory cytokines. Also an unbalance in the expression of M1 and M2 has been identified in RA, as the polarization toward M1 is also induced by the presence of ACPA, and IRF5 produced by Th17 and Th1 cells.[58]

The recruitment of monocytes and MCs into the synovial tissue is a key step in the development of RA. In a normal synovial tissue, the proportion of MCs is lower in comparison to the presence of FLS. This proportion is inverse in patients with RA. Monocytes and MCs in patients with RA also produce chemokines to increase the recruitment of leukocytes to the joints. An important amount of monocytes express CD68 in surface, which is a scavenger receptor involved in cell–cell interactions. It has been observed that the proportion of CD68-positive MCs is correlated with the radiological progression of the disease.[59]

The interaction between monocytes, MCs, and ACPA has been clarified in recent years. ICs that contain citrullinated proteins, specially fibrinogen, and ACPAs are potent stimulants of TNF-alpha production by MCs, through FcyR IIa receptor. Also, ICs with the presence of citrullinated histones increase the production of TNF-alpha through FcyR IIa receptor and TLR4. ACPAs induce the expression of IRF4 and IRF5, which polarize MCs to the M1 subset. Also, the high expression of macrophage colony-stimulating factor (M-CSF) in the inflammatory environment induces the expression of ACPA-sensitive MCs expressing CD16 and CD163, which are able to produce higher amounts of TNF-alpha and IL-1B. These cytokines promote the induction of Th1 and Th17 subsets.[60]

There is an increased interest for the study of the role of lactoferrin in RA. It has been observed that lactoferrin-containing ICs are able to increase the production of pro-inflammatory cytokines. The expression of anti-lactoferrin antibodies has been identified in several autoimmune diseases, such as RA. Regarding the role of monocytes, recent studies show that lactoferrin-containing ICs are able to induce the production of TNF-alpha and IL-1B from monocytes. This is accomplished by the stimulation of FcyRIIa and Mcd14 receptors present in the surface of these cells. Lactoferrin-containing ICs could be one of the factors responsible for perpetuating the local inflammatory process.[61]

Natural Killer Cells

NKCs have a pro-inflammatory role but also act as immune regulators in the pathogenesis of autoimmune diseases. Opposite to the expectation, NKC numbers are decreased in both RA and SLE patients apparently due to the influence of cytokines in this pro-inflammatory environment.

In one of the first studies about the relationship between NKC and RA, it was found that there was a decreased activity of NKC in the blood, synovial fluid, and synovial membrane of RA patients compared to healthy controls.[62] Also they determined that there were less of these cells in RA patients, and their numbers did not decrease when methotrexate, D-penicillamine, and azathioprine were given, but they did when piroxicam was given.[62–64] In a recent study with unpublished results, they found that, apparently, patients treated with etanercept had an increased expression of NKC, suggesting an immunomodulatory role of this drug.[65]

Subsequently, they examined the possible immunomodulatory functions of NKC and found that a phenotype of NKC (Leu 11-b) present on the synovial fluid was downregulated in patients with RA. Then, these cells were incubated with complement, and after they were lysed, there was an increase in levels of IgG and IgM antibodies both in the synovial fluid cells and in peripheral blood cells, suggesting a possible protective role of NKC over antibody production and severity of the disease.[66]

In 1991, Hendrich et al. analyzed NKC activity in RA patients, and they found that cytotoxicity and antibody-dependent cell-mediated cytotoxicity (ADCC) were decreased. When normal NKCs were cultivated with ICs of RA patients in vitro, there was an induced change in the structure of the membrane-bound FC gamma RIII, a decrease in NKC activity, and a loss of ADCC capacity. This confirms the modulating role of NKC and the great pathogenic role of ICs in the disease.[67]

This previous concept was understood later by the identification of receptors that contain both activating and inhibitory forms of NKC, for example, the killer cell inhibitory receptors (KIR), which were first defined as an inhibitory receptor but subsequently found to play both roles, like the exclusive KIR2DL1-3 (CD158a and CD158b) inhibitors. This was further complemented by Pridgeon et al.,[68] who studied the presence of CD158a and B receptors in synovial fluid NKCs of RA patients, finding a decreased expression of these receptors compared to control subjects (more than 90% of the patients' NKC lacked CD158a/b receptors). These findings contrast with the possible utility of the receptor FcgRIII (CD16) present in NKC and MCs as a parameter to determine the disease activity, which correlates with the number of NKC in RA patients, although the

proportion of this NK/macrophage marker was different between patients.[69]

Despite the evidence supporting a possible immunomodulating role of NKC in RA, there is a pro-inflammatory interaction of these cells with FLS present in the joints of patients with RA. This relationship promotes the activation, cytokine production, and survival of NKC through cytokines produced by FLS such as IL-15.[70] NKC also could co-stimulate B cells and T cells in the joints (though this is not proven in RA), contributing to the activation of MCs and FLS, and stimulate osteoclast differentiation.[71] Furthermore, while NKC population expressing CD158 is diminished, there is an increase in NKC expressing CD56 in RA patients with CD56 bright phenotype (a phenotype characterized by high production of IFN-γ), which could contribute to a higher pro-inflammatory environment.[72]

Recently, a new set of cells with similar functions as NKC were discovered, and they are still considered a part of the innate immunity. These are the natural killer T (NKT) cells that play an important role in the induction of the humoral response by B cells. NKT cells are highly active in patients with RA, inducing the production of IL-4 and IFN-γ, which unlocks the differentiation process of B cells from the marginal zone in the spleen, to became plasmablast. This overstimulation induces an override in B-cell tolerance and increases their production of autoantibodies.[73]

Neutrophils

Traditionally, NTs are considered to play its role in the innate effector function of the immune system, but this is not their only feature. They represent 80% of the cell population in the joints of RA patients.[74] It was always thought that the fundamental role of NTs in RA was the secretion of pro-inflammatory factors and enzymes that mediated joint damage. It was observed that joint NTs are activated by cytokines that modulate their responses to ICs.[75] Also, the majority of circulating NTs in RA patients are in a "readiness state" to rapidly produce reactive oxygen species if stimulated by certain factors, in contrast to a healthy person's NT.[76]

In 2003, Cross et al. postulated a new function for NT in RA patients. They documented that in these patients, NT isolated from peripheral blood contained a significant amount of MHC II mRNA, and NT isolated from synovial fluid also had the ability to express MHC II in their membranes, though with low expression of co-stimulatory molecules. The authors suggest that NT response to factors within their local environment could change their molecular properties and enable them to acquire the ability to perform new functions. This function of NT was also assessed in patients with psoriatic arthritis and SLE, but results were negative. Also the NTs of RA patients were capable of stimulating T cell proliferation in vitro.[77] Furthermore, peripheral NTs from healthy subjects, when cultivated in an RA patient's synovial fluid, made a trans-differentiation into DC-like cells.[78]

Besides the interesting findings listed above, NTs from RA patients are also capable of expressing RANK/RANKL pathway proteins, so they could be able to intervene in bone remodeling.[79]

The NTs in RA patients are characterized for having FcyRIIa receptors that intervene in respiratory burst signaling, and in the liberation of proteolytic enzymes and inflammatory mediators; however, when patients are treated with infliximab, the expression of these receptors decreases and the expression of FcRIIb2 inhibitory receptors increases and lasts up to 3 months after treatment.[80]

NTs also exhibit other interesting features that may contribute to the pathogenesis of the disease, including the secretion of oncostatin M and B lymphocyte stimulator (BLyS),[81] and the expression of citrullinating enzyme PADI4, which could have a role in the formation of citrullinated peptides.[82] In addition, greater amounts of secretion of vascular endothelial growth factor (VEGF) have been demonstrated by the NTs in RA patients, which may contribute to the formation of pannus by neovascularization, a characteristic feature of the disease.[83]

Finally, RA NTs have greater life spans than in healthy people. This may be due to intrinsic alterations of the synovial pro-inflammatory environment. Similarly, this retardation in apoptosis may be improved with early methotrexate treatment.[84]

Dendritic cells

DCs are the bridge between the innate and adaptive immunity, where they play a fundamental role in RA pathogenesis. These cells have been proposed as the cells that present the arthritogenic antigens to T cells, generating the initial response of adaptive immunity. There are two types of DCs: conventional or myeloid dendritic cell (mDC) and plasmacytoid dendritic cells (pDCs). In RA, the most important ones are the mDCs. The pDCs have a controversial role because they can have pro-inflammatory or tolerance induction function.

In RA patients, studies have not found a higher number of DCs than in healthy controls.[85] However, there are differences in the type of DCs present. In synovial liquid, there is predominance of immature DCs, and in synovial tissue, there is a major number of mature DCs.[86] These cells could be the source of DCs that after maturation move to the synovial tissue, contributing to the chronicity of inflammation.[87]

The DCs present in the joints of RA patients tend to lead the inflammatory response more to T helper 1 lymphocytes (Th1) than T helper 2 lymphocytes (Th2). This takes more importance because it was found that only the DCs that are present in the joints have this property, and the ones in the bloodstream are weak inductors of Th1 cells response. Because of this, it has been proposed that the place where DCs acquire the capacity to activate T cells is within the joint.[88]

Meanwhile, Radstake et al. described the influence of the activation of DC through certain receptors. When the DC activation is realized through FcyR receptors, the response is more anti-inflammatory than when is realized by independent mechanism of FcyR. With FcyRIIb occurs a decrease in pro-inflammatory cytokine production such as IL-6, TNF-alpha, and IL-12, and increase in the IL-10 levels. Also the chemokine production is decreased by the DC. That is the reason why this DC activation mediated by FcyR has been proposed like a possible therapeutic target.[89] This receptor is increased in patients with quiescent RA.[90]

The DC activation can also occur through TLR through recognition of DAMPs and PAMPs. Specially, activation is done through TLR type 3, 4, 7, and 8, which leads to more cytokine production from DC, contributing to a more pro-inflammatory environment.[91]

Other cells

The bone and joint damage in RA is not exclusive of the cells from the immune system; the native cells from joints also cause this damage. Far from being victims of immune activation, the FLS and osteoclasts contribute to RA pathogenesis.

FLS are mesenchymal cells also called type B synoviocytes. Usually, their function is to produce extracellular matrix and synovial liquid components, maintaining joint homeostasis. In RA joints, FLS are not only increased in number, they also produce molecules that broke down extracellular matrix, recruit leukocytes from blood, activate them, and promote their survival maintaining the chronic inflammation that is characteristic of this disease.[92] In fact, it is proposed that FLS are the main effectors of the joint damage by means of invasion and metalloproteinase production.[93]

Recent evidence, using animal models, shows that in an environment with inhibition of the endogenous p53, the invasiveness and proliferation of FLS were increased, suggesting a possible presence of somatic mutation in the *p53* gene that could play an important role in the hyperplasia and cartilage damage generated by these cells.[59]

One of the proposed pathways for the activation of these FLS is through chemokines, which have an influence not only on cell migration as previously believed, but also on gene transcription of some cells. Immune cells are not the only ones that express chemokine receptors, considering that several tissue cells can express them, including FLS. In RA patients, it was found that FLS express chemokine receptors: CXCR3, CCR2, CXCR4 and CCR5, allowing them to respond to stimulus mediated by the following chemokine: macrophage inflammatory protein 1 (MCP-1), interferon-inducible protein 10 (IP-10), stromal cell-derived factor 1alpha (SDF-1alpha), and monokine induced by interferon-gamma (Mig) (CCL2, CXCL10, CXCL12, and CXCL9, respectively). These chemokines are produced by infiltrating cells from immune system and also by FLS. This stimulus leads to further migration and FLS proliferation that in turn leads to an increased production of degrading enzymes of extracellular matrix like gelatinase and collagenase. These findings support that chemokines have a more active role in RA pathogenesis than it was believed, and established them as new therapeutic targets.[94]

In addition to chemokines, especially through CXCR3 receptor, there are other molecules involved in FLS proliferation, like macrophage MIF and other cytokines like TNF-alpha and IL-1B.[95]

FLS also have a wide interaction with the infiltrating cells of the joints. For example, it was found that FLS express IL-17 receptors, whose ligand is mainly produced by Th17 cells, that have been related to autoimmunity,[96] resulting in the production of pro-inflammatory cytokines by FLS like IL-6, and IL-8, among others.[97]

FLS can produce cytokines that activate different leukocytes, like IL-15 and IL-17, inducing proliferation of T cell and B cell, increased cytotoxic activity from T cells and NKC, production of immunoglobulin, and prevention of T cells apoptosis.[98]

FLS in RA patients also present phenotypical differences in comparison to the FLS in healthy people. One of the main differences is that they have lost the contact inhibition, which contributes to the proliferation of FLS. A recent finding suggest that the inhibitor of DNA binding (Id1), which is a nuclear protein that regulates cell growth, is highly expressed in the vascular tissue and synovial fluid, as it is produced by FLS. Free Id1 acts as a potent inductor of angiogenesis.[59]

The role of metabolic changes present in FLS of patients with RA has gained relevance. It has been observed that the presence of high pressure and hypoxic environment of the joints in patients with RA induces a phenotypical change in FLS, making them more aggressive and active. These cells present an accelerated glucose metabolism through the upregulation of glycolysis. The stimulation of FLS with TNF and platelet-derived growth factor (PDGF) increases the glucose metabolism and the expression of GLUT-1. Also, the hypoxic environment promotes the activation of glycolysis that gives support for angiogenesis. Lactic acid, as a product of glycolysis, is a potent inductor of tissue invasion for the FLS. The FLS from patients with RA express high levels of hexokinase 2 (HK2), which is associated with the production of glucose-6-phosphate. The high expression of HK2 provides FLS resistance against apoptosis.[99]

Osteoclasts are the cells responsible for bone remodeling under physiological conditions. At the inflammatory environment of RA, they are primarily responsible for bone erosion. In normal conditions, the osteoclasts are activated by the pathway of the activator receptor of NF-kB (RANK) and RANK-ligand (RANKL). RANKL normally is expressed by osteoblasts, which in turn activate osteoclasts; however, in RA, this molecule can be expressed by other cells like T helper cells and FLS,[100] stimulated by pro-inflammatory cytokines like TNF-alpha, IL-1, IL-6, IL-17 leading to

non-controlled osteoclast activation. Also, infiltrating B cells present at synovial tissue are important source of RANKL in patients with RA.[101]

Osteoclast also expresses a high preference to bind with ACPA. Recent evidence shows that ACPAs are able to recognize citrullinated proteins in the surface of osteoclast. However, the ACPAs are not stimulating them. Osteoclast expresses PAD enzyme and citrullinated proteins through the entire differentiation process, indicating that citrullination is required for osteoclast differentiation and metabolism. So, as RA induced an increase citrullination, this could explain the increased presence of osteoclast in the synovial tissue.[60]

Mast cells are granulated tissue resident cells, with an important role in the first response against antigens. They express pattern recognition receptors to sense the presence of antigens and initiate the appropriate response. They produce several substances that include histamine, TNF-alpha, and VEGF in response to their activation, and as a consequence, local vascular permeability and edema are generated. They also produce chemokines for the recruitment of granulocytes. Regarding RA, mast cells appear to be increased in number in synovial tissue of patients with RA. Their role in the pathogenesis of the disease could be considered as ambiguous. The presence of ACPA ICs generates the activation of mast cells in the synovial tissue. As a consequence, a pro-inflammatory response is engaged: histamine, VEGF, leukotrienes, and prostaglandins (PGs) increase vascular permeability and angiogenesis. Histamine, IL-1, IL-6, PDGF, and IL-13 induce the activation and hyperplasia of fibroblasts. They also induce osteoclast differentiation and activation through the production of TNF-alpha, IL-1, and RANKL. They increase macrophage activation through IFN-γ and IL-6 production, and also the recruitment and activation of NTs through CXCL8/IL-8 production. However, they also exert an immunomodulatory action that includes suppression of the migration and activation of DCs, reduced production of pro-inflammatory cytokines by MCs and NTs, and inhibition of Th1 differentiation. So, as confusing as this could be, the hypothesis is that the role of mast cells is dependent on the phase of the disease they are acting. However, more evidence is required to elucidate this.[102]

The innate lymphoid cells (ILC) are involved in the initial immune response before the recruitment of adaptive immune cells. They are important in the response against pathogenic organisms, tissue homeostasis, and regulation of metabolism. These cells can be divided into three groups depending on the transcription factors they required, their function, and the cytokines they produce. Group 1 ILC (ILC1) includes NKCs, CD127+ILC1 cells, and CD103+ILC1 cells; they produce IFN-γ in response to IL-12, IL-15, and IL-18 stimulation. They are involved in the immune response against viruses, intracellular bacteria, and protozoa. Group 2 ILC (ILC2) is characterized by their need of GATA3 transcription factor and their production of Th2-inducing cytokines such as IL-4, IL-5, and IL-13. They are involved in the response against helminths, in tissue repair, and in the regulation of lipid metabolism. Group 3 ILC (ILC3) is characterized for their requirement of RORyt and IL-7 for their development and functioning. They are involved in the response against extracellular bacteria, in tissue repair, and in the development of lymphoid tissue. Regarding RA, it has been observed that ILC3 cells are increasingly expressed in the synovial fluid of patients. They produce high levels of TNF-alpha and IL-22, which induce the proliferation FLS. Also ILC1 are associated as they produce high amounts of IFN-γ in response to the presence of IL-2, IL-12, and IL-15.[103]

Complement system

In RA, the complement pathway has been studied since the 1950s, when a group of researchers started to measure the complement levels in synovial fluid and plasma of patients with RA, finding contradictory results. Apparently, levels of complement in serum are elevated while levels in synovial fluid of patients with RA are lower compared to healthy people or people suffering from another type of joint disease, suggesting the activation of CP and the utilization of complement proteins to increase local inflammation. Increased levels of late complement degradation products were found in synovial fluid from RA patients.[104] Later, the alternative pathway (AP) was also involved, when it was found that levels of factor B and properdin were diminished in RA patients,[105] which can be stimulated apparently by type II collagen.[106] Recently, the cartilage oligomeric matrix protein (COMP), a protein that stabilizes tissue structure of cartilage, has been discovered as a new trigger for the activation of the AP probably as a result of cartilage breakdown and interaction with properdin.[107]

This enhanced activation of the CS can also be related to the diminished expression of regulatory complement proteins like the C3 convertase regulators (CD55, CD46, CD35) found in NTs of RA patients,[108] and the upregulation of the expression of complement receptors in the membrane of monocytes in patients with RA.[109]

Furthermore, some researchers proved that synovial tissue was capable of producing CS proteins,[110] and that it was also deposited in the papillary dermal vessels of affected and non-affected skin biopsy samples from RA patients, suggesting a possible role in the development of rheumatoid vasculitis.[111] Subsequently, Hurst et al. found defects in the complement-mediated phagocytosis in patients with rheumatoid vasculitis, which could explain the deposition of ICs around blood vessels and the development of type III hypersensitivity.[112]

Complement degradation products have also been correlated with levels of RF,[113] activity of the disease,[114] and extra-articular manifestations.[115] Treatment of the disease with corticosteroids can reduce the expression of complement proteins.[116] Recently, it was shown also that treatment with infliximab reduced the complement activation, possibly

by reducing the levels of C reactive protein (CRP).[117] CRP is one of the most important markers of disease activity, and it has been shown to trigger the activation of the CS. In RA, this activation is increased by CRP, especially in patients with active disease.[118]

Also the ACPA auto-antibodies can act as a trigger for the activation of classic and AP.[119] It has been observed that ACPAs are able to activate the complement in a dose-depending way to act through any of the two pathways. The IgM, IgG1, and IgG3 isotypes are the most potent activators. IgG and IgM activation favor the CP.[60]

Recently, Watanabe et al. discovered that high-density lipoprotein (HDL) molecules from RA patients contain altered proteins of the CS such as factor B, C3, and C9, among other pro-inflammatory proteins like acute phase proteins. This suggests the possible mechanism by which the HDL losses its anti-inflammatory properties and helps to increase the risk of cardiovascular disease in RA patients.[120]

Toll-like Receptos

TLRs are pattern recognition receptors associated with the recognition of PAMPs and DAMPs. Some of them are expressed in extracellular environment and others in intracellular environment.

TLR2 and TLR4 are extracellular receptors that are highly expressed by MCs and fibroblasts present in the synovial tissue of patients with RA. Efforts have been made for the detection of SNPs of TLR2 and TLR4 genes; however, evidence is not conclusive. It has been observed that TNF and IL-17 induce the expression of TLR5, also an extracellular receptor, in monocytes and MCs of patients with RA. Levels of expression of TLR5 are correlated with disease activity. TLR3 and intracellular receptor have also been associated with RA. An increased expression of TLR3 is associated with a more severe disease activity. The increased expression of TLR3 is due to the production of IFN-alfa. Regarding TLR7, it has been established that the presence of RNA residues in synovial fluid could induce the production of TNF by monocytes in patients with RA.[121]

Microbiome

In recent years, a significant amount of research has been directed toward the study of the role of microbiota in the development of autoimmunity. Evidence has shown that gut and lung microbiota are crucial elements in the homeostasis of the immune response. An adequate balance on the components of microbiota is required in order to maintain healthy immunity. Loss of this balance due to the presence of different bacteria or due to overgrowth of certain species (dysbiosis) is associated with the loss of immune tolerance and, as a consequence, the development of autoimmunity.[122]

In RA, three sites of dysbiosis have been associated with the development of the disease: lung, oral, and gastrointestinal mucosa. The processes that occur in these mucosa generate the loss of tolerance against citrullinated molecules, which trigger the immune response. The role of periodontitis is known for being associated with the development of systemic inflammation. The presence of *Prevotella intermedia* and *P. gingivalis* is associated with increased production of IgG. *Prevotella spp.* suppresses the production of joint-protective type 2 cytokines and expresses enzymes with amino deiminase activity that increase citrullination and, as a consequence, the production of ACPAs in people with a genetic predisposition. Also, there is evidence of the local production of ACPAs in lung biopsies. The exposure to environmental particles such as the ones in the cigarettes induces the expression on PAD which is responsible for citrullination of proteins that induce the production of autoantibodies. Evidence of citrullination processes at the gut is also available; there is an increased expression of citrullinated vimentin in colonic tissues of patients with RA. In murine models, the disruption of intestinal microbiota increases the production of pro-inflammatory cytokines, especially IL-17, which activates and induces the differentiation of B cells into a phenotype capable of producing autoantibodies that initialize the process of a chronic inflammatory state.[122]

Systemic Lupus Erythematosus

Macrophages

Although, in recent years, the knowledge about the alterations in the immune system of patients with SLE has increased, the specific role of monocytes/MCs into its pathophysiology is unclear. However, a number of known alterations affecting the normal functions of MCs could contribute to SLE, such as T cell activation, antigen presentation, phagocytosis of apoptotic bodies, and cleaning of ICs.

It has been found that patients with SLE have an increased Fas-ligand dependent MC apoptosis,[123] and also their ability for phagocytosis is altered, which may play an important role in the development of SLE.[124] According to this model, the altered phagocytosis of apoptotic bodies and altered cleaning of ICs increase the amount of autoantigens in tissues that can trigger immune response with further tissue damage, which in turn increases the number of apoptotic bodies, becoming a vicious circle. This could be one of the most likely triggers for the beginning of the autoimmune process. It has been found that in the germinal centers of lymph nodes, there is an inadequate cleaning by MCs, and therefore, there is an increase in the number of autoantigens that bind to follicular DC, which leads to generating output signals for the production of autoreactive B lymphocytes (BL) and losing tolerance to the own antigens.[125] The autoantibody production against molecules such as the scavenger receptor A (important in clearance of apoptotic bodies) has

been described as one of the factors that disturbs the equilibrium of self-tolerance by altering the clearance of apoptotic bodies in vitro and could play an important role in SLE pathogenesis.[126] It has also been described that the reduced clearance of apoptotic bodies by the MC is associated with decreased levels of some complement factors.[127]

The role of MCs, particularly when they are activated, becomes especially important when renal compromise in SLE is discussed. It is known that MC infiltration and proliferation is a significant feature of renal pathology, especially in its most aggressive forms, and amplifies kidney damage.[128] Furthermore, the expression of myeloid-related protein (MRP) types 8 and 14, indicators of MC inflammatory activity, is increased in various forms of glomerulonephritis such as LN.[129] Similarly, PGs like thromboxane A2 (TXA2) alter renal function when it is increased in the glomerulus. Expression of the *COX-2* gene (cyclooxygenase) is increased in MCs from patients with active LN, unlike those with inactive LN or healthy patients, a feature not found in other nephropathies; in fact, this is considered specific for LN and it has been postulated as possible therapeutic target for SLE.[130] Finally, monocyte-related molecules, such as neopterine, CD14, among others, have been found elevated in patients with LN and they have been postulated as markers of monocyte activation in these patients.[124] In a similar way, nitric oxide is produced in larger quantities by monocytes from patients with LN, which could alter the function of T lymphocytes (TL).

Regarding the production of cytokines in SLE, MCs play an important role as well, producing smaller amounts of IL-12 and increased amounts of IL-10, which modulate cytokine production[131] like IL-6, which has an important role in the differentiation of cells secreting IgG.[132] This alters the functioning of BL, favoring the increase in levels of autoantibodies, because excess of IL-10 induces greater production of Ig and reduces levels of IL-12 that normally control the number of antibody-producing cells. Likewise, it has been documented that IL-1 production by MCs in SLE patients is reduced, especially in those with high disease activity, which has a direct effect on the proliferative capacity of the TL.[133,134] The chemotactic molecules for MCs are also diminished in SLE patients.

The antigen-presenting and lymphocyte activation functions of normal MCs are altered in SLE. A decrease in the amount of monocytes that express HLA-DR, which plays a fundamental role in increasing T cell proliferation, has been described.[135] The expression of surface molecules such as CD80 and membrane receptors for the Fc portion of IgG also has been altered in patients with SLE.[136] Studies have also shown that monocytes from patients with SLE cultivated with T cells of patients without SLE induced an altered proliferative response of T cells through the monocytes interaction.[137] Furthermore, previous research has shown that serum from patients with SLE has IgG and IgM that alter the antigen-presenting function of MCs that contribute to a lower antigenic response in these patients.[138]

Recently, through the examination of splenic tissue from patients with SLE, a reduction in the expression and phagocytic function of the marginal zone MCs was observed, which are implicated in the clearance of apoptotic cells and induction of tolerance through the production of TGF-B and IL-10. Also, a recently discovered mechanism of autophagy was identified, and it is known as microtubule-associated protein 1A/1B-light chain 3-associated phagocytosis (LAP). It facilitates the phagocytosis of dying cell debris. In animal models with deficiency of these mechanisms, lupus-like syndromes were developed.[139]

Natural Killer cells

The role of NKCs in the pathophysiology of SLE remains unclear. It is known that in patients with SLE, the number is diminished and their cytotoxicity is impaired,[140] which in turn could generate insufficient production of cytokines required for the regulation of IgG production.[141] Huang et.al. found a decreased number of NKCs in SLE patients compared to healthy controls, especially the CD226-positive NKC (17% vs. 88%, respectively). These values gradually turned back to normal as patients reached remission.[142] However, IFN-alpha (which is elevated in SLE patients and is related to disease activity and severity[143]) has been postulated as an important factor for the decrease of NKC, because it mediates activation of cell death pathways in patients with active SLE.[142] After being activated by IFN-alpha, NKCs infiltrate renal tissue in murine models and cause damage through the production of cytotoxic granules and pro-inflammatory cytokines.

Similar to NKC CD226+, NK CD3-CD56+CD16+ cells are decreased in SLE patients and present an altered expression of NKG2A and NKG2D, which may have a role in the pathophysiology of the disease.[144] This concept was found controversial in a recent study.[145]

On the contrary, it has been found that NK T cells (CD4-CD8-CD57+) from SLE patients are increased in quantity and produce more IL-4, an important cytokine in the pathogenesis of SLE, compared to healthy subjects or individuals with infectious disease. This might suggest that this specific cells may have an important role in the disease pathogenesis.[146]

Recent studies have found that NKCs in patients with active SLE have the ability to produce large amounts of IFN-γ, a cytokine that has been associated with cytotoxicity provided by overexpression of MHC class I and class II molecules.[145]

NKCs also have been used as biomarker for clinical response to rituximab in patients with RA and SLE, because there is an increase in the number of NKCs after initiating therapy with this drug.[147]

NKCs express killer immunoglobulin-like receptors (KIRs) that are associated with the production of pro-inflammatory cytokine and in the modulation of immune response. An imbalance between activating and inhibitory KIRs is

associated with increased susceptibility in the development of autoimmune processes.[148]

Neutrophils

The role of NT in the pathophysiology of SLE has become more clear in recent years. Currently, it is known that NT can respond against own cells in SLE patients through a cell death mechanism that plays an important role in innate immune response to an infection called NETosis. In this mechanism, NTs liberate neutrophil extracellular traps (NETs), an anti-microbe mechanism made of peptides, DNA, histones, and NT proteins.[149]

Normally, NET responds against microorganism, but in SLE, patients can respond against their own cells. Also, it is known that NET-producing NTs are capable of inducing endothelial damage and infiltrate the tissues of SLE patients.[150] It is also known that in some SLE patients, NET degradation is altered, generating a series of mechanisms inside pDCs and NTs that perpetuate autoimmune processes and have been found to be associated with SLE manifestations such as LN.[151] Recent studies have demonstrated that anti-microbe peptide (LL-37), which functions as a DC activator in psoriasis, and human neutrophil peptide (HNP) are increased in SLE patients.[149,152] They both induce more NET liberation, stimulating autoreactive B cells to begin the production of antibodies against LL-37, HNP, and NT DNA. These antibodies along with NET liberation constitute a strong stimulus for pDCs to activate and increase IFN-alfa production that increases NT LL-37 production, which in turn increases NETosis, cell death, and NET production, generating an endless cycle that expands and perpetuates inflammation.[153]

Recent publications have begun to question the role of NETosis as a sufficient trigger for SLE, and the management of lupus clinical manifestations by inhibiting it.[154] That is the reason why Liu et al. tried to establish whether post-transcriptional histone modifications were capable of inducing antibody production against histones, and they concluded that isolated exposition to NETs is insufficient to alter tolerance mechanisms in cells, so there must exist other additional factors.[155] Other studies have demonstrated how the serum of patients with active SLE has reduced capacity of degrading NETs in vitro, a function that is slowly restored as the disease reaches remission.

Also, the serum levels of complement factors C3 and C4 are decreased in this group of patients. Similarly, in vitro NETs activate CS and deposit C1q, resulting in the inhibition of NET degradation, and therefore promoting the characteristic SLE antibody production.[156] Furthermore, it has been documented that SLE patients' NTs have a reduced capability to recognize and remove C1q/calreticulin/CD91 apoptotic bodies.[157]

A study from Chauhan and colleagues evaluates the NET degradation efficiency and the NT-mediated phagocytosis in three groups of patients with SLE (group 1: express anti-dsDNA, group 2: express ENAs, group 3: express both anti-dsDNA and ENAs). They found that patients who express anti-dsDNA had an impaired capacity for NET degradation, while a reduction in the phagocytosis activity was present in all patients. This finding is relevant regarding the pathogenesis of LN, considering that in patients with renal compromise, there is an increased production of NET. Considering anti-dsDNA deposits in renal tissue, this could generate a reduction in the degradation of NET. So, this imbalance could be responsible for a perpetuation of the inflammatory process in the kidney.[158]

Denny et al. described a group of pro-inflammatory NT called low-density granulocytes that are capable of producing type 1 IFN (like IFN-alpha), TNF-alpha and IFN-γ; they also alter the differentiation of endothelial cell progenitor and, with that, the capacity to become mature endothelial cells. They are capable of damaging endothelium directly. This is why these cells are postulated to have an important role in the development of cardiovascular disorders in SLE.[159]

Proteins such as neutrophil gelatinase-associated lipocaline (NGAL), specialized molecule to bind and transport small hydrophobic molecules such as iron, have been postulated as potential biomarker of kidney function in patients with SLE, with a sensitivity and specificity of 66%–89% and 62.5%–87.5%, respectively[160]; however, recent publications did not find such association.[161]

Another way in which NTs have been involved in the loss of peripheral self-tolerance is through the self-activation of TLR2/TLR4 by nucleosomes (the major SLE autoantigens) phagocytosed by the NT. This induces NT production of IL-8, which in turn will stimulate NT recruitment and DC activation. Finally, this leads to an increase in the production of nucleosome-based self-antigens that are presented to self-reactive T cells altering peripheral tolerance.[162]

In addition, NTs are constantly producing reactive oxygen species. It has been found that IgG constant fraction receptor (FcyR)-mediated superoxide anion (O2–) production is related to the appearance of some SLE clinical manifestations.[163]

Recent data suggest that anti-La antibodies may act as NT function modulators in SLE patients, apart from being responsible for the characteristic SLE neutropenia.[164]

Dendritic cells

In general terms, SLE patients have a decreased number of mDCs than healthy controls, especially mDC DC11+, an essential molecule for LT immunophenotyping, as well as the migration and activation from leukocytes.[165,166] mDCs play an important role in the induction of immune adaptive response, inducing central and peripheral tolerance, and are capable to phagocyte and process necrotic material and apoptotic bodies without being attached to ICs. Instead, the

pDCs are only capable to phagocyte apoptotic bodies if they are bound to antibodies (generally autoantibodies), as it was mentioned previously. This leads to an increased production of IFN-alpha[167] and upregulation of inflammatory gene expression.[168]

The function of pDCs has been documented as being altered in SLE patients, either by the huge number of pro-inflammatory signals in the environment or intrinsic defects of these cells that induce an altered response to stimulus.[169] Jin et al.[170] found that pDCs from SLE patients have an increased ability to activate and induce proliferation of T cells, in contrast to the pDCs from healthy patients, even in the absence of apoptotic bodies, which is the major stimulus for the IFN-alpha production from these cells. In addition, in healthy controls, the pDCs that phagocytized apoptotic bodies induced the production of regulatory T cells, a fact that did not happen in pDCs from SLE patients. Besides, the pDCs presented a decreased IL-6 production, a decreased expression of IL-18 mRNA, and a persistent IL-10 synthesis after phagocyte apoptotic bodies from NT in SLE patients. The role of IL-18 in the pDC function has been described in renal glomerulus of SLE patients. This IL induces the migration of pDCs to glomerulus, decreasing its number in blood, causing that pDCs activate resident LT promoting renal damage.

Regarding mDCs, it is known that they present an altered phenotype in SLE patients, characterized by an accelerated differentiation and maturation, as well as increased secretion of pro-inflammatory cytokines. This has been explained by the major expression of CD1, CD80, CD86, HLA-DR, and IL-8.[171] Also, it was described that in SLE patients, these cells present a decreased endocytic capacity, which in turn is correlated with lower expression of mannose receptors and could be influenced by IFN-γ present in the environment.[172] It deteriorates the phagocytic function from DC and alters the immunological homeostasis, like mentioned above, to increase the autoantigens capable of inducing the autoantibody production. Nie et al.[173] described that in SLE patients, the DC derived from bone marrow induced by FMS-like tyrosine kinase 3 ligand (Flt3), a small molecule that acts as a growth factor that increases the number of immune cells, express higher CD40 and CD86 levels and induce T cell proliferation more strongly than in healthy controls.

Also, as mDCs located in the lymph nodes are involved in the maintenance of peripheral tolerance through the regulation of T cells, it has been identified that the presence of IFN-alfa increases the expression of TLR7 mRNA, potentiating the antigen-presenting activity of these cells. This action favors the probability of presentation of self-antigens.[174]

Mice with SLE in which DCs are extracted present a decreased disease activity, in addition to a decrease in the number of regulatory and inflammatory T cells. So it was shown that in SLE, the DCs are not required for initial activation of T cells and B cells; however, they do promote their proliferation and are essential in the progression of tissue damage. This is why DCs have been postulated as a potential therapeutic target for this disease.[175]

It is also known that the balance between activator and inhibitor signals determines the function of DC, which may be regulatory or stimulatory. Studies have evaluated whether DC stimulated with inhibitory signals induces a regulatory function that can stop the SLE progression and activity. Zhang et al. found that the stimulation of immature DC with ICs inhibited notably the DC maturation by means of lipopolysaccharides or CpG, improving the tolerance through the FcyRIIb activation, and induced the PGE-2 production from DC, which together decreased the T cells response. As a result of this, the administration of DCs that overexpress FcyRIIb has been proposed like possible alternative to decrease SLE progression.[176] In addition, vitamin D is known as a molecule that contributes to restore the balance in immune response by inhibiting DC maturation and activation.

These findings, when taken together, support the important role that DCs play in pathophysiology of RA and SLE, besides opening the possible targets for therapeutic intervention and trying to lead DCs to a tolerogenic phenotype.[177]

Basophils

The role of basophils in SLE has gained importance in recent years. These cells are associated with the production of IL-4 and other cytokines required for the expression of Th2 cells. There is evidence in animal models that Th2 early expression dependent on basophils and IgE stimulation was involved in the development of LN. When the mice were depleted on basophil and IgE expression, the production of autoantibodies and kidney injury were lower. Also the expression of plasma cells was lower. This finding suggests that basophils could be involved in the amplification and maintenance of autoreactive B cells in the kidney. Increased expression of IgE was associated with the overstimulation of basophils.[178]

Pan and colleagues in 2017 published a study in which they investigated the role of basophil activation in the development of SLE. They observed that patients present decreased levels of basophils in blood, but they present higher activity than the basophils of healthy individuals. As it was stated before, they also found an increased expression of autoreactive IgE, and an increased expression of the high affinity receptor for IgE FcεRIα in the surface of basophils. The reduced amount of basophils in blood was explained by the fact that in SLE, they rapidly migrate to lymph nodes and the spleen, mediated by an increased expression of CD62L and CCR7. They also observed that basophils interact directly with B cells by inducing them to differentiate into an antibody-producing B cell. In addition, basophils are capable of inducing Th-17 differentiation through an increased production of IL-17.[179]

Other cells

FLS have not been associated with the production of arthritis in patients with SLE. In SLE patients, the pathophysiological mechanisms of arthritis, which is characterized by the absence of severe bone erosions or damage that may lead to deformities, have not been studied in depth. However, it is known that an IFN-inducible overexpression of genes occurs and also a decreased expression of genes involved in extracellular matrix homeostasis[180] that, as mentioned before, is believed to play a role in the pathogenesis of the type of arthritis that occurs in SLE.

Actually, the role of IFN-alpha as a negative regulator in osteoclastogenesis is very well known. It was proposed that IFN-alfa controls the erosive versus non-erosive phenotype in SLE patients. In addition, recent studies in SLE patients suggest that through IFN-alpha, the myelopoiesis diverts toward differentiation from monocytes to DC instead of osteoclast in murine models.[181] This explains why autoimmune diseases like SLE present a non-erosive arthritis unlike RA.

Complement system

The complement pathway plays an essential role in the development of autoimmune diseases, especially in SLE. Main functions include chemotaxis of leukocytes, opsonization, clearance of ICs, cell lysis, and sensitization of adaptive immune response.

Several publications have related the CS to SLE pathogenesis. There has been a decrease in the activation of the three CS pathways, CP, lectin pathway (LP), and alternative pathway (AP), in patients with active SLE.[182] Further, it is known that in this disease, it plays a dual role: on one hand, it has a protector role facilitating the clearance of ICs and apoptotic cells, and intervening in tolerance mechanisms. On the other hand, it has a pathogenic role by perpetuating the progression of local inflammation contributing to tissue damage.[183] Thus, deficiencies and alterations in several complement components have been associated with the pathogenesis of some autoimmune diseases such as SLE. Moreover, the treatment addressed to the inhibition of certain complement components has also showed beneficial effects in SLE treatment in murine models.[184]

Clearance of apoptotic bodies and cellular debris. The role of the CS within SLE physiopathology related to this function has already been described along this review. It is known that alterations or absence of C1q, responsible for initiating complement cascade through its interaction with apoptotic bodies, cellular debris, IgG, IgM, and acute phase proteins,[185] is linked with an impaired clearance of cellular debris and apoptotic bodies by immune cells.[127,182,186] C1q deficiencies are rare; however, when they occur, they can generate SLE in 90% of the patients[186] by cellular mechanisms not clearly known yet. As it was mentioned, when the role of MCs was discussed, Bijl et al. described that the impaired clearance of apoptotic bodies and cellular debris from these cells is associated with lower levels of C1q, C3, and C4 and is not an intrinsic defect of the cell, supporting the major role of these molecules in the clearance of apoptotic bodies.[127]

Clearance of ICs. The complement binds to ICs and keeps them for increasing their size, maintaining their solubility, and providing ligands that facilitate the clearance of them by phagocytes.[183] Santer et al. propose that unlike what happens in normal individuals in which the monocyte-MCs clean the antibodies bound to self-antigens quickly through C1q function, in C1q-deficient patients, these complexes are cleaned less efficiently by monocyte-MC, leading to increased participation of pCD, which results in an increased IFN-alpha production as was mentioned previously. Once this happens, the increased IFN-alpha in the cellular environment turns pCD more resistant to C1q inhibition.[185] This affirmation controverted the results of another study published 1 year before.[187] In turn, Arason et al.[188] described defects in IC precipitation and deposit in SLE patients correlated with lower levels of C4a; however, in a posterior study, they found that only lower levels of C4a do not explain this alteration and other mechanisms are required to compromise this CS function.[189] Besides, in murine models, Factor H deficiency has been described as a factor that accelerates LN development.[190]

Tolerance and immune response. This CS function is tightly related to apoptotic body clearance. When the apoptotic body clearance is impaired by deficiency or abnormalities in complement function, the presence of a prolonged apoptotic body in tissues occurs. This could generate secondary necrosis and leads to DC maturation with inflammatory response activation and loss of tolerance to self-antigens.[183] However, it is known that this alteration is not only sufficient to impair self-tolerance, even in SLE patients.

Moreover, the antibodies against complement components have been implicated in SLE physiopathology too. Antibodies to C1q (anti-C1q) were found increased in SLE patients.[191] Further, these have been correlated with renal compromise in these patients, including several activity index, which postulate them as potential LN biomarkers such as anti-dsDNA and markers such as C3 and C4.[192] Several theories have been proposed about their pathogenic role in SLE, especially LN. Anti-C1q could improve the C1q-mediated apoptotic body clearance; Bigler et al. found that these antibodies are directed specifically to C1q bound to apoptotic cells in earlier stages of apoptosis and do not to C1q bound to Ig or ICs. This would establish a direct link between apoptosis, C1q, and SLE development.[193] Other studies suggest that anti-C1q can interfere with complement activation, altering IC solubilization and making difficult their recognition and

clearance by immune cells, and contribute to the circulating IC formation that are deposited in the kidney of SLE patients. However, it is recognized that their pathogenic role in this disease depends on the C1q levels in the glomeruli and the amount of IC in it.[194]

By the same way, antibodies against mannose-binding lectin, which start the LP, are involved in apoptotic bodies and cellular debris phagocytosis through binding to calreticulin and CD91 from phagocytes and have been found elevated in SLE patients compared to healthy controls (15% vs. 3.6%, respectively), especially those with quiescent disease.[195] Thus, these antibodies have been proposed as possible implicated in SLE pathogenesis or autoimmunity perpetuation in SLE patients.

Toll-like Receptors

The intracellular TLR9 is associated with the increased production of IFN-alfa by plasmacytoid DCs through the detection of ICs. These cells also detect them through TLR3 and TLR7. However, it is interesting that the activation of TLR9 decrease the production of IFN through TLR7. It has been observed that women present a stronger activation of TLR7 and, as a consequence, higher levels of IFN, compared to men who have more expression of TLR9. Further investigation on this concept is required.[196]

Intracellular TLR9 has also been associated with the increased expression of B lymphocyte stimulating factor (BLyS) in murine models with SLE. Expression levels of TLR9 and BLyS were increased in mice with SLE, which indicates that TLR9 activation may induce the expression of BLyS and, as a consequence, increase the inflammatory response triggered by B cells.[148]

In recent years, an important role of these receptors in the pathogenesis of LN has been found. Extrinsic and intrinsic DAMPs, especially the ones present in the kidney, are capable of activating TLRs on infiltrating monocytes and DCs, increasing the production of cytokines by these cells. Mesangial cells express TLR1-4 and TLR6 and are activated by ICs that contain DAMPs, contributing to the development of glomerulonephritis. TLR2 and TLR4 are also expressed by parenchymal cells, NTs, MCs, and DCs. When they are exposed to HMGB1, a lupus autoantigen, they induce the activation of NF-KB. Podocytes also express TLR4, and by the induction of a pro-inflammatory environment, the barrier function of them became disrupted. The inflammatory environment in the kidney stimulates the expression of TLR3, increasing the production of IL-6, especially in the presence of high levels of estrogen. This could explain the increased risk present for women. Also, TLR3 increases the production of CXCL1 that acts as chemoattractant of NTs. TLR7, TLR8, and TLR9 expressed by plasmacytoid DCs present in the kidney react to the presence of DNA residues. Their activation induces the production of type 1 IFN, increasing the local immune response.[197]

Microbiome

Regarding the role of microbiome dysbiosis in SLE, there is not enough conclusive evidence. However, some studies may suggest the role of the microbiome in the pathophysiology of the disease. Manfredo and colleagues reported that translocation of a commensal bacterium such as *Enterococcus gallinarum* from the small intestine to the liver in murine models induces the production of Th17, which increases the production of IFN-1 and anti-dsDNA antibodies. Supporting this observation, reports of liver biopsies from patients with SLE and autoimmune hepatitis have shown the presence of *E. gallinarum*. Another study shows that patients with SLE have intestinal colonization with bacteria that express the orthologous RNA-binding protein Ro60 (autoantigen present in SLE), favoring the positive selection of autoreactive T cells and B cells in patients. Finally, it has been observed that patients with SLE and Sjögren's syndrome present a less diverse gut microbiome compared to healthy controls, but the oral microbiome present in both groups of patients was different. Gut microbiome may be the one determining the type of autoimmune compromise. However, more evidence is required in order to support these observations.[198]

Limitations of the review

This review is the result of exhaustive literature research made by the team in order to develop a full compilation of the latest findings made by different research teams regarding new pathophysiological mechanisms associated with the development of RA and SLE. The search was centered on components of innate immunity, as it is a topic that usually is not addressed, due to the focus on adaptive immunity. This article presents to the reader an up-to-date compilation of the role of innate immunity in these pathologies, and it could open new opportunities for future research on this topic.

However, some limitations could be identified in this review. One of them is that the literature search was limited to indexed publications present in MEDLINE PubMed, and no other medical literature databases were included this time. Also, only publications in English language were reviewed, and this issue could have let some information in other languages outside of this work. These limitations will be taken into account for future reviews.

Conclusions

Although the adaptive immune system has a determinant role in the development of autoimmune diseases such as RA and SLE, the study of innate immune system role in those diseases acquires high importance if the functions from the cells that compose it are taken into consideration. The role of this system in RA and SLE pathophysiology is especially important in early stages; however, it is fundamental to

maintain the immune response and the disease progression. This is possible not only by the relationship between cells of this system, but also by the relationship between innate and adaptive immune system. That is why detecting alterations in normal function of these cells, besides improving the knowledge of autoimmune diseases physiopathology, could help to establish different ways to interfere the natural history of them.

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