Ministry of Higher Education

and Scientific Research

University of Diyala

College of Medicine

A Review Article in:

Pathogenesis of systemic lupus erythematosus

Submitted to the Council of the College of Medicine, Diyala University, In Partial Fulfillment of Requirements for the Bachelor Degree in medicine and general surgery.

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Abstract

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, with multisystemic involvement. There are numerous phenotypes of the disease, with clinical symptoms ranging from modest mucocutaneous signs to multiorgan and severe central nervous system involvement in patients. SLE is a chronic disease with a waxing and waning history, severe morbidity, and the potential for death in some people if not treated early. Despite major improvements in pathophysiology and medical care optimization, patients with SLE still have a high mortality rate, are at risk of increasing organ damage, and have a lower health-related quality of life. The etiology and susceptibility are poorly understood and the pathogenesis is multifactorial and complex. In these papers we reviewed literature to emphasize the pathogenesis and pathological processes of the disease.

Keywords: lupus, pathogenesis, apoptosis

Introduction

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease, with multisystemic involvement. There are numerous phenotypes of the disease, with clinical symptoms ranging from modest mucocutaneous signs to multiorgan and severe central nervous system involvement in patients. In the development of SLE, several immunopathogenic pathways play a role (1). In Latin, the word *lupus* means "wolf bite," as the disease's debilitating effects were reminiscent of wolf bites (2). Moriz Kaposi (1837–1902) was the first to recognize lupus as a systemic disease with visceral features. Osler in Baltimore and Jadassohn in Vienna helped to establish the systemic form. Other significant milestones include Reinhart and Hauck's (1909) description of

the false positive syphilis test in SLE; Libman and Sacks' (1923) description of endocarditis lesions in SLE; Baehr's (1935) description of glomerular changes; and Klemperer, Pollack, and Baehr's (1939) use of the term diffuse connective tissue disease (1941). The discovery of the 'LE' cell by Hargraves, Richmond, and Morton at the Mayo Clinic in 1948 marked the start of the contemporary era of SLE (3-5). Lupus prevalence rates in the United States are believed to be as high as 51 per 100 000 people. In the last 40 years, the incidence of lupus has nearly tripled, owing to better detection of mild disease. Incidence rates in North America, South America, and Europe are estimated to be between 2 and 8 per 100 000 per year. Women are nine times more likely than men to be impacted, and African American and Latin American mestizos are substantially more likely than Caucasians to be affected, with higher disease morbidity (6). SLE is a chronic disease with a waxing and waning history, severe morbidity, and the potential for death in some people if not treated early. The disease begins with a preclinical phase marked by autoantibodies similar to other systemic autoimmune disorders and progresses to a clinically overt autoimmune phase that is more disease-specific (7).

Figure 1. SLE

Despite major improvements in pathophysiology and medical care optimization, patients with SLE still have a high mortality rate, are at risk of increasing organ damage, and have a lower health-related quality of life. New technologies have made it possible to classify SLE sooner, and customized early intervention and therapy strategies aimed at clinical remission or low disease activity may help to prevent damage and improve long-term outcomes. (8). In this short review, we will review the latest hypothesis about the etiology, pathogenesis and how the disease affect other organs.

Literature review

Systemic lupus erythematosus (SLE, or lupus) is a multi-organ inflammatory autoimmune disease. Pathogenic autoantibodies directed against nucleic acids and their binding proteins are produced in SLE, indicating a widespread lack of self-tolerance. In the context of environmental triggers and stochastic events, the loss of tolerance and subsequent immunological dysregulation is a result of genetic variables, with new research linking over 30 genetic loci in disease pathogenesis (9). B cells from SLE patients show a lack of self-tolerance as well as an abnormal overproduction of antibody. The immunological characteristic of SLE is the presence of antinuclear autoantibodies (ANA). ANA testing is frequently utilized in clinical practice as part of an initial investigational screen. The presence of anti-DNA antibodies is a far more specific result than a positive ANA, which is observed in 98 percent of individuals with SLE. Anti-DNA antibodies are seen in around 60% of SLE patients (10). The specific involvement of anti-DNA antibodies in lupus is still a matter of debate. Many patients' serial serum concentrations of these antibodies reflect disease activity, but not all. It is now obvious that some anti-DNA antibodies are actually harmful, rather than only

acting as a disease marker. Injecting human hybridoma-derived anti-DNA antibodies into severe combined immunodeficiency (SCID) mice, for example, results in antibody deposition in the kidneys and proteinuria in some circumstances. Many questions, however, remain unsolved. Because some people have strong antiDNA antibody levels but no signs or symptoms of illness (11). A range of additional autoantibodies, in addition to anti-DNA antibodies, are frequently found. The antigens addressed may be linked to patient ethnicity (for example, Afro-Caribbean individuals have higher levels of anti-Sm antibodies), or specific illness symptoms (for example, anti-Ro antibodies seen in association with a photosensitive rash). Finally, antiphospholipid antibodies are frequently identified in lupus patients, whether or not they have the associated clinical illness (12).

The development of SLE is heavily influenced by genetic predisposition. Although a single gene defect (e.g. C1q) can cause this in rare circumstances, it is more typically caused by the combined impact of a large number of genes (13). Each allele has a minor effect (odds ratio 1.5), and it is thought that the aggregation of multiple genes is required to considerably enhance the risk of SLE. The processes by which risk alleles contribute to autoimmunity and the combinations of risk alleles that lead to susceptibility are poorly understood. In fact, the majority of single nucleotide polymorphisms (SNPs) linked to SLE are found in noncoding DNA and serve as markers for co-segregated alleles. Despite this, the majority of them are linked to genes that are thought to be involved in the immunological response (14). During the past few years, genome-wide analyses have substantially increased the number of candidate genes associated with SLE. Their function is variable. Some, such as IRF5, STAT4, osteopontin, IRAK1, TREX1 and TLR8, are involved in nucleic acid sensing and interferon (IFN) production, whereas others are involved

in T cell (PTPN22, TNFSF4, PDCD1) or B cell (BANK1, BLK, LYN) signaling pathways (e.g. PTPN22 regulates lymphocyte activation). BCL6 is the lineage-specific transcription factor of follicular helper T cells (TFH), a T cell subset that provides help to B cells in germinal centers. Interestingly, IRF5 and STAT4 additively increase the risk of SLE. Some genes have been associated with several autoimmune diseases (e.g. STAT4 with rheumatoid arthritis; PTPN22 with rheumatoid arthritis and diabetes), yet others appear to specifically increase the risk of SLE (15).

SLE has been linked to a variety of neutrophil abnormalities in the past. Neutropenia can affect a large percentage of SLE patients at some time during their illness. The C1q/calreticulin/CD91-mediated apoptotic pathway is unable to remove lupus neutrophils, and they have aberrant oxidative activity. Low-density granulocytes are a unique granulocyte population found in lupus patients (LDGs). These cells are found in mononuclear cell fractions after density separation, have increased ability to produce proinflammatory cytokines, such as type I interferons (IFN-I), and are hazardous to endothelial cells. Importantly, even in the absence of additional stimulation, lupus LDGs are prepared to produce excessive NETs. LDGs externalize increased quantities of autoantigens and immunostimulatory chemicals by generating enhanced NETs (16-18). *Palanichamy et al* (19) found that neutrophils in the bone marrow are the principal producers of IFN-I, as well as the B-cell activating cytokines A proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF). In addition, when compared to peripheral blood, IFN-I signals were stronger in bone marrow. The aberrant B-cell morphologies found in SLE may be due to alterations in

pre- and pro-B cells, as well as T1/T2 transitional B cells in the bone marrow, which have a strong IFN signature (19).

Growing evidence suggests that different cytokines play a critical role in the pathophysiology of SLE. These cytokines are soluble molecules that play an important role in immune cell development, maturation, and activation (20). Because of its tight relationship with B lymphocytes, IL-6 was one of the first cytokines to be examined in the pathophysiology of SLE. Monocytes, fibroblasts, and endothelial cells are the main producers of this cytokine, but T- and B- lymphocytes also contribute to its production. It has a complex interaction with other cytokines, as IL-1, IL-2, and tumor necrosis factor-a (TNF-a) increase its levels while IL-4, IL-10, and IL-13 decrease them (20).

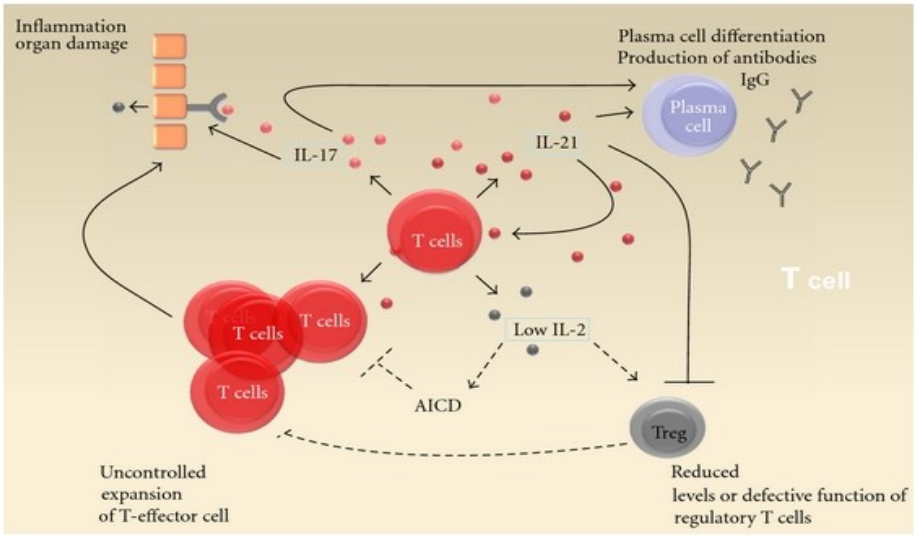

Figure 2. Diagram about the effect of cytokines in lupus

Serum IL-6 levels were found to be favorably linked with disease activity and anti-DNA levels in human lupus patients. In vitro, IL-6 was found to be elevated in lymphoblastoid cells from lupus patients, and blocking IL-6 resulted in a decrease in anti-dsDNA. When compared to

healthy individuals, B cells retrieved from SLE patients produced more circulating immunoglobulins on their own. This spontaneous immunoglobulin secretion was considerably reduced by IL-6 inhibition, but was restored by exogenous IL-6 treatment. It was discovered that B cells from lupus patients produced anti-dsDNA on their own, and that this ex vivo autoantibody synthesis was primarily released by low density B lymphocytes (21).

Patients with SLE have higher levels of circulating IL-17 and IL-23, and this elevation correlates with disease activity. One of the earliest cytokine abnormalities in autoimmune disorders was an increase in type I interferon in lupus patients. The relationship between IFN levels and disease activity, as well as anti-dsDNA levels and clinical symptoms, supports IFN's participation in SLE pathogenesis. Plasmacytoid dendritic cells (PDC) were found in the dermal lesions of lupus patients and are responsible for continuous IFN release, despite their low circulating quantity in the peripheral blood. PDC migration to the glomeruli is seen in lupus nephritis patients, and this movement is hypothesized to be controlled by IL-18 (22).

Several research have looked at the levels of tumor necrosis factor-a in SLE patients. TNF-a levels were found to be significantly higher in these investigations when compared to healthy controls. Although most investigations have found higher TNF-a levels in the blood, the clinical relevance of this rise is unclear. TNF-a levels were found to be greater in SLE patients with active disease in several investigations examining the beginning of SLE in adults (23).

In patients with SLE, the complement cascade is frequently activated, resulting in hypocomplementemia and complement component

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deposition at sites of tissue damage, particularly in the renal glomeruli and the epidermis. Complement activation is thought to play a role in tissue destruction in SLE, according to this data. Complement is also involved in the formation of the autoimmune response in SLE, although it appears to play a protective role in this scenario, as evidenced by the high incidence of SLE in people who are genetically defective in early components of the classical complement activation pathway (24).

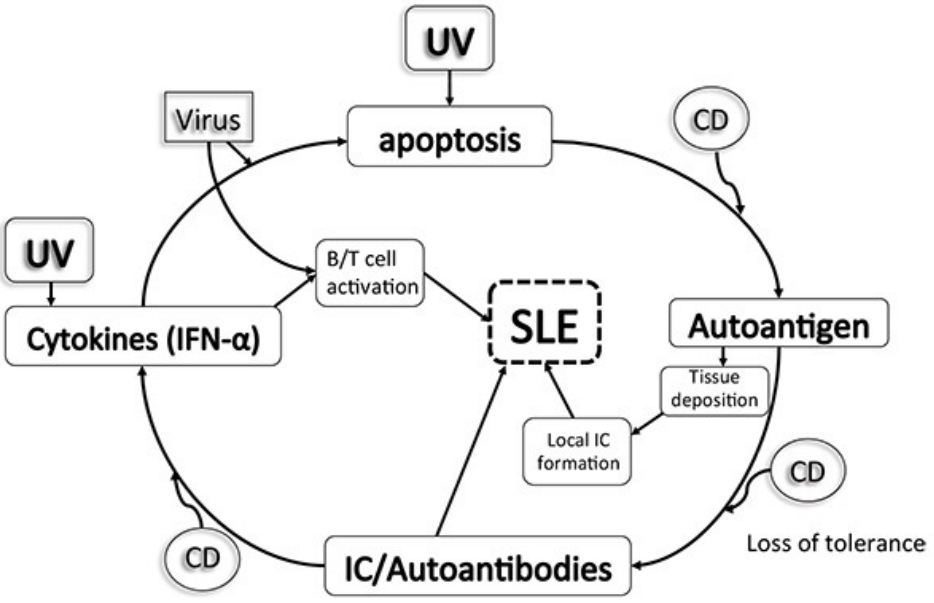

Figure 3. Complement cascade in lupus

In patients with SLE, increased apoptosis and/or poor clearance of apoptotic material has been discovered, and the resulting higher apoptotic load is linked to the disease's onset and severity. These cells develop secondary necrosis and disintegrate into apoptotic blebs due to poor clearance of apoptotic cells. Many chromatin alterations occur during apoptosis, including caspase, endonuclease, or granzyme B breakage, as well as the addition or removal of covalently linked moieties via acetylation, methylation, phosphorylation, ubiquitination, citrullination, ADP ribosylation, or transglutamination (25). Dendritic cells are effective

phagocytes of apoptotic material and the most potent antigen-presenting cells for the activation of (naive) T cells after maturation. DC maturation can be promoted by ligation of CD40 and a variety of pathogen associated molecular patterns (PAMPS), which are detected by DCs via TLRs and other pattern recognition receptors (PRRs). However, endogenous TLR ligands, such as damage associated molecular patterns (DAMPs), have been discovered in addition to external TLR ligands (26). The ability of these DAMPs, as well as apoptotic blebs and modified autoantigens, to stimulate DC maturation has been demonstrated. When DCs catch apoptotic T cells, the level of CD40 ligand (CD40L) expression, which is enhanced by activating stimuli, influences DC maturation (27). Studies indicating that treatment of myloid DCs loaded with apoptotic or necrotic cells can trigger the production of antinuclear antibodies in normal and lupus mice demonstrate the importance of DCs delivering apoptotic material in the pathogenesis of SLE. Furthermore, vaccination with these DCs exacerbated the severity of the disease in lupus mice (28).

T cells from SLE patients have different levels of cellular activation. Increased intracytoplasmic calcium flux and cytosolic protein tyrosine phosphorylation are signs of TCR CD3 engagement, which results in an early and amplified signaling response. In SLE T cells, the CD3 complex is rewired, with the CD3 chain being replaced by the FcRg common chain. The signal relies on the spleen tyrosine kinase (Syk) rather than the conventional z-associated protein ZAP-70 when FcRg is present (29). The accumulation of lipid rafts on the cell surface is another component that contributes to increased T cell activation. When a cell is activated, these high-cholesterol membrane zones rich in signaling chemicals polarize. A study found that injecting a medication that enhances lipid raft clustering

accelerates illness onset in a murine model of lupus (MRl/lpr), whereas injecting a drug that disrupts lipid raft clustering has the reverse effect (30).

The fact that clinical concordance of SLE in identical twins is confined to less than half of the pairings demonstrates the importance of the environment in the manifestation of SLE. Environmental factors linked to SLE have also been linked to epigenetic changes such as DNA methylation. UV exposure is an established risk factor for clinical disease, and various environmental pollutants, including smoking, have been linked to clinical disease in epidemiological research (31). In patients with SLE, viral infections such as parvovirus B19 and cytomegalovirus (CMV) are frequent. Much of the debate has concentrated on the possibility that SLE is caused by a viral infection. Although the great frequency of EBV in the adult population makes it difficult to draw conclusive conclusions about causality, substantial evidence that EBV precedes SLE development was shown in a study that looked at serum samples from individuals before and after they developed lupus (32).

Oral contraceptives have little effect on SLE illness flares, despite the fact that hormones can alter autoimmune development in mouse models. Pregnancy aggravates SLE in general, but not because of an increase in estradiol or progesterone levels; in fact, SLE patients' levels of these hormones are lower in the second and third trimesters than healthy pregnant women. Surprisingly, in comparison to healthy men, a large number of men with SLE have greater estradiol levels and lower testosterone levels (33).

Conclusion

SLE is progressive serious disease with complex pathology and etiology, its pathogenesis is multifactorial but mainly to B cells lack of

tolerance and excessive production of anti-nuclear antibodies. The etiology need more researching in hope to find a modifiable cause.

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