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Review

The cryptic interplay between systemic lupus erythematosus and infections

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ABSTRACT

The underlying trigger for systemic lupus erythematosus (SLE) has remained elusive, and multiple interacting environmental and genetic factors likely contribute to the onset and perpetuation of the disease. Among environmental influences, infectious agents have been suggested to play a pivotal role in driving autoimmunity pathogenesis via structural or functional molecular mimicry, the expression of proteins that induce cross-reactive responses against self-antigens, and the aberrant activation or apoptosis of different immune system cells in the context of a peculiar genetic background. The increased viral load and changing subsets of lytic or latent viral proteins observed in selected populations with SLE have indicated that common viruses, such as Epstein–Barr virus, parvovirus B19, cytomegalovirus, retroviruses and transfusion-transmitted viruses, might be triggers for this disease. Alternatively, some infectious agents might exert a protective effect from autoimmunity. Existing achievements have not been fully investigated and clarified. Thus, the aim of this review is to analyze the medical literature within the last 15 years regarding the role of infectious agents in the pathogenesis of SLE.

Contents

1. Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder characterized by widespread immune dysregulation and the hyperproduction of multiple autoantibodies and immune complexes, resulting in chronic systemic inflammation and potential damage to a variety of organs [1]. The natural history of SLE ranges from an insidious slowly progressive disease, with exacerbations and remissions, to an acute and rapidly fatal disease. Patients often display constitutional symptoms, such as fever, fatigue, anorexia, myalgia, and weight loss, at both the onset and during exacerbations of this disease [2,3]. The overall outcome is highly variable, ranging from remission to the risk of death. Recent epidemiological evidence has clearly shown that short/medium-term survival rates have greatly improved in the last decade, although the long-term prognosis still remains poor [4]. Approximately 15–20% of patients develop symptoms before 18 years of age, and the disease affects 5000–10,000 children and adolescents in the United States, with prevalence rates varying between 3.2 and 250 per 100,000 in different populations, with more common results observed in native Americans, Afro-Americans and Asians [5–10]. Girls are more frequently affected, with a sex ratio of approximately 4:3 before puberty

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and 4:1 after puberty. Although this disease can occur at any age, SLE is more frequently observed after five years, becoming increasingly prevalent after the first decade of life [5,11,12]. Juvenile SLE is typically more aggressive than adult SLE, showing a substantially higher prevalence and severity of renal and/or central nervous system involvement, requiring higher doses or sustained treatment with corticosteroids and other immunosuppressive medications [13,14]. Pediatric SLE is primarily associated with increased mortality and reduced remission rates, although the prognosis of this disease has markedly improved over the past few decades, with a 10-year survival rate exceeding 90%, which is comparable with that in adults. The major causes of death include renal disease, severe disease flares with significant organ damage, and infections [1,4]. The SLE diagnosis is based on the criteria from the American College of Rheumatology 1982/1997 and the more recent Systemic Lupus International Collaborating Clinics (SLICC) classification 2012, which retain the old specificity while being more sensitive (Table 1) [15,16]: a patient is classified as having SLE if four or more criteria, including at least one clinical and one immunological criterion, are present either serially or simultaneously, during any interval of observation, in the absence of another explanation. The SLE etiopathogenesis remains largely obscure, and genetic, environmental, and hormonal factors contribute to the disease susceptibility. In generic terms, SLE occurs when an environmental trigger induces an immunological dysfunction in a genetically predisposed individual, leading to the loss of tolerance towards native proteins. Among environmental factors, a growing body of experimental and clinical data supports a pivotal role for infections in the induction, onset, perpetuation and/or exacerbation of SLE [17–21]. The aim of this review is to conduct an analytical appraisal of the medical literature, published in the last 15 years, concerning the role of infectious agents in the pathogenesis of SLE.

2. The association with infections

Viral, bacterial, parasitic or fungal infectious agents can be responsible for aberrant immune response in genetically prone individuals [18]. Accordingly, several studies have attempted to examine and clarify the association between infections and autoimmunity, and a number of hypotheses have been formulated. Different mechanisms, in which an "infector" molecule contributes to the pathogenesis of autoimmune diseases, have been proposed. Table 2 shows the mechanisms associated with the activation of autoreactive T and B cells, mediated through different infectious agents. Molecular mimicry is based on the incorporation of epitopes structurally similar to self-antigens through the infecting agent; this structural resemblance confuses the immune system, generating an autoimmune response. Viral and bacterial superantigens bind to the variable domain of the T cell receptor beta chain and a wide variety of major histocompatibility complex (MHC) class II molecules, interacting with different subsets of T cells, irrespective of their specificity, and inducing a network of autoimmune reactions. Epitope spreading reflects the exaggerated local activation of antigen-presenting cells, causing both overprocessing and overpresentation of antigens, followed by the priming of large numbers of T cells, which might encourage the development of an autoimmune process. Bystander activation is associated with enhanced cytokine production, inducing the expansion of autoreactive T cells, whose number was insufficient to produce an overt disease. The polyclonal activation of lymphocytes through lymphotropic viruses might result in enhanced antibody production and circulating immune complexes, causing damage to self-tissues. The altered apoptosis of the host cells and exposure of masked antigens to the immune system through a given microorganism are other mechanisms that might induce immunological dysfunctions. Furthermore, genetically determined deficits in the immune system might lead to the insufficient clearance of infectious agents, whose persistence in the host might contribute to autoimmunity. Emerging evidence has suggested that the production of autoantibodies

Table 1
The Systemic Lupus International Collaborating Clinics (SLICC) 2012 classification criteria for systemic lupus erythematosus (SLE).

Criterion	Definition
Clinical criteria	
Acute cutaneous lupus	Malar rash, Bullous lupus, Toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, Photosensitive lupus rash (in the absence of dermatomyositis) *or* Subacute cutaneous lupus (non-indurated psoriasiform and/or annular polycyclic lesions that resolve without scarring, although occasionally with dyspigmentation or telangiectasias)
Chronic cutaneous lupus	Discoid rash (localized or generalized), Hypertrophic (verrucous) lupus, Lupus panniculitis (profundus), Mucosal lupus, Lupus erythematosus tumidus, Chilblain's lupus *or* Discoid lupus/lichen planus overlap
Oral or nasal ulcers	In the palate, buccal mucosa and tongue *or* In the nasal mucosa (in the absence of other causes, such as vasculitis, Behçet's disease, herpes virus infection, inflammatory bowel disease, reactive arthritis, etc.)
Nonscarring alopecia	Diffuse thinning or hair fragility with visible broken hairs (in the absence of other causes such as alopecia areata, androgenic alopecia, iron deficiency, or drug-induced alopecia)
Synovitis	Involving 2 or more joints, characterized by swelling or effusion *or* Tenderness in 2 or more joints and at least 30 min of morning stiffness
Serositis	Typical pleurisy for more than 1 day, *or* pleural effusion, *or* pleural rub Typical pericardial pain (with recumbency improved by sitting forward) for more than 1 day, *or* pericardial effusion, *or* pericardial rub, *or* pericarditis documented by electrocardiography (in the absence of other causes, as infection, uremia, Dressler's syndrome, etc.)
Renal involvement	Urine protein-to-creatinine ratio (or 24-hour urine protein) showing 500 mg protein/24 h, *or* Red blood cell casts
Neurologic involvement	Seizures, Psychosis, Mononeuritis multiplex (in the absence of other known causes, such as primary vasculitis), Myelitis, Peripheral or cranial neuropathy (in the absence of other causes, such as primary vasculitis, infection, diabetes mellitus, etc.) *or* Acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, etc.)
Hemolytic anemia	
Leukopenia or lymphopenia	Leukopenia (<4000/mm^3 at least once) in the absence of other known causes, such as Felty's syndrome, drugs, and portal hypertension *or* Lymphopenia (<1000/mm^3 at least once) in the absence of other known causes, such as corticosteroids, drugs, and infection
Thrombocytopenia	<100,000/mm^3 at least once—in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura
Immunological criteria	
Anti-nuclear antibodies (ANA)	Level above the laboratory reference range

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