

The pathogenesis of systemic lupus erythematosus

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ABSTRACT

SLE is a complex, heterogeneous disease, the precise pathogenesis of which remains something of a mystery. In recent years our understanding has been advanced by the development of novel genetic and immunological techniques. Susceptibility to SLE has a genetic component and multiple putative genes are being investigated. The genes involved are likely to play a part in immune regulation. Central to the immune dysfunction seen in SLE is the presence of autoreactive B cells, which predominantly target nuclear antigens. In addition to evidence of aberrant B and T cell behaviour, lupus is associated with complement deficiencies, and abnormal cytokine function. A number of environmental triggers exist, and likely candidates include viral infection and exposure to UV light. Finally, evidence is accumulating that implicates apoptosis as a mechanism by which disease may be provoked and propagated.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune rheumatic disease, characterised by the presence of autoantibodies. Virtually every organ or system can be involved, but commonly, SLE affects the skin, joints, haemopoietic system, kidneys, lungs and central nervous system. There is no simple answer to the question 'what causes lupus?' This heterogeneous disease is caused by the complex interaction of a variety of abnormalities which cause disease susceptibility, and/or provoke disease onset or exacerbation. At the core of this process is immune dysfunction, and the production of autoantibodies.

AUTOANTIBODIES

B lymphocytes from patients with SLE display a lack of self-tolerance, and an inappropriate overproduction of antibody. The presence of antinuclear autoantibodies (ANA) is the immunological hallmark of SLE. In clinical practice, ANA testing is often used as part of an initial investigative screen. A positive ANA is a sensitive test, found in 98% of patients with SLE,¹ but the presence of anti-DNA antibodies is a much more specific finding. Anti-DNA antibodies are seen in approximately 60% of patients with SLE.¹

The precise role that anti-DNA antibodies play in lupus remains an area of great interest. Serial serum concentrations of these antibodies reflect disease activity in many patients, but not all.² Instead of simply acting as a disease marker, it is now clear that some anti-DNA antibodies are, in some way, directly pathogenic. For example, studies have shown that injecting human hybridoma-derived anti-DNA antibodies into severe combined immunodeficiency (SCID) mice results, in some cases, in renal deposition of antibody with associated proteinuria.³ However, many questions remain unanswered. Since some patients have high anti-DNA antibody levels without overt disease, what are the critical structural features which determine pathogenicity? In addition, some patients have severe disease without detectable anti-DNA antibodies, so does this imply a different mechanism of disease?

In addition to anti-DNA antibodies, a variety of other autoantibodies are often detected. The antigens targeted may be associated with patient ethnicity (for example, increased levels of anti-Sm antibodies seen in Afro-Caribbean patients),¹ or particular disease manifestations

(for example, anti-Ro antibodies seen in association with a photosensitive rash). Finally, patients with lupus are often found to have positive antiphospholipid antibodies, with or without the related clinical syndrome.

THE GENETICS OF SLE

There is clearly a genetic component to disease susceptibility in SLE. Early evidence in support of this theory came from epidemiological studies of affected twins – monozygotic twins have a concordance rate of about 25%, compared with 2% in dizygotic pairs.⁴

More recently, genome wide screening has been used in an attempt to localise lupus susceptibility genes. This area is highly complex and there is considerable variation in the reported results. This variance may in part reflect methodology, but may also reflect the true diversity seen. The genes encoding HLA antigens would seem obvious potential targets, and in the Caucasian population, there does seem to be an association between HLA-DR2 and HLA-DR3.⁵ Interestingly, however, this association is not necessarily seen in other ethnic groups. A second area of potential linkage is mapped to the chromosome 1q region, which seems to stand out in affected sibling pair studies.⁶

It seems likely that the genes implicated will have immune functions. Areas of interest include genes that encode proteins involved in antigen presentation (the HLA genes), apoptosis, the Fc receptor, B and T cell function, and the production of cytokines and complement.

IMMUNE DYSFUNCTION AND SLE

B cells and T cells

Central to the immune dysfunction seen in SLE is the existence of overactive B cells, which produce an abundance of autoantibody. The development and survival of these cells is dependent upon T-cell help. The propagation of self-directed B-cell clones may also be assisted by an inappropriate lack of T-cell suppression.

B-cell activators, such as the protein B-lymphocyte stimulator (BLyS), appear to be upregulated in lupus, further encouraging B-cell survival.⁷

Powerful new evidence for the strength of the role of B cells in disease development comes from a recent study of B-cell depletion therapy in patients with SLE, resistant to conventional therapies.⁸ Although only a small number of patients have been treated so far, results suggest a beneficial response in the majority.

There is good data to show that immune cell signalling is abnormal in SLE.⁹ Stimulation of lupus B and T cells results in abnormally high free intracellular calcium

concentrations and increased production of tyrosine phosphorylated proteins. This inappropriate response may account in part for the 'overzealous' behaviour of these cells.

Complement

Complement is involved in the clearance of immune complexes, and its function is somehow intertwined with the development of lupus. The association between genetic complement deficiencies and the development of lupus triggered early speculation about a possible role for complement in the aetiology of SLE.¹⁰ Furthermore, it was observed that in patients with SLE, complement consumption, with falling serum concentrations, often mirrors disease activity.

With the increased interest in apoptosis (see below), the contribution of complement has become a hot topic once again. Defective clearance of apoptotic fragments may provide the link between complement dysfunction and SLE.¹¹

Cytokines

Cytokines are low-molecular-weight proteins which act as the chemical modulators of the immune system. It is easy to hypothesise, therefore, that they would seem a good potential site for dysfunction and, moreover, a convenient therapeutic target. Below, a selection of putative candidates are discussed.

IL-10 is secreted by T-helper cells, and stimulates B-cell proliferation and antibody production. There is an increasing body of research to suggest that this cytokine may be central to the overproduction of antibody seen in SLE. The serum concentration of IL-10 in lupus patients is significantly higher than that seen in normal controls.¹² Stimulating lupus mononuclear cells with IL-10 causes significantly increased production of antibody.¹³ Moreover, SCID mice, injected with mononuclear cells from SLE patients and then treated with anti-IL-10 antibodies, display a marked reduction in the production of autoantibodies.¹³

Tumour necrosis factor α (TNF α) has also been investigated, and the evidence suggests that it may be protective against lupus. Linkage studies have demonstrated an association between low TNF α inducibility and an increased incidence of lupus nephritis, through the DR2 genotype.¹⁴ Conversely, DR3-positive patients have relatively high TNF α production, and are not predisposed to nephritis. The development of anti-TNF α drugs has provided a new angle on the hypothesis that blocking TNF α may be involved in the pathogenesis of SLE. The use of both of the commercially available anti-TNF α drugs, etanercept¹⁵ and infliximab,¹⁶ has been associated with the development of anti-DNA antibodies and, more rarely, a lupus-like syndrome.

However, other data suggest that the role of TNF α may not be so straightforward. For example, in a study looking at renal biopsies from patients with grade III and IV nephritis, approximately 50% of the samples exhibited TNF α deposition,¹⁷ suggesting a positive role in disease pathogenesis. Transforming growth factor β (TGF β) is involved in the differentiation of CD8+ T cells into cells that downregulate the production of antibody. Ohtsuka *et al.* have looked at the function of TGF β in lupus.¹⁸⁻²⁰ Initial studies revealed that constitutive and active levels of TGF- β were decreased in these patients, when compared with controls. Moreover, treating lymphocytes collected from SLE patients with TGF β resulted in the suppression of IgG production. Implying, therefore, that impaired secretion of TGF β may in part account for the overproduction of antibody seen in lupus.

APOPTOSIS

In recent years, there has been growing interest in the role that apoptosis plays in the development of autoimmunity. Casicala-Rosen *et al.* demonstrated that the intracellular components that often make up the spectrum of target autoantigens in lupus cluster in blebs on the surface of apoptotic cells.²¹ This position enables them to be presented as antigen. Apoptosis is, however, a physiological process. Its part in the development of autoimmunity must, therefore, be dependent upon dysfunction elsewhere. In a recent editorial, Charles describes research findings that could account for this.²² Essentially, apoptotic fragments are usually rapidly cleared, minimising the production of an immune response. If, however, the rate of apoptosis overwhelms this function, or clearance is suboptimal, immunogenicity is increased.

Thus, apoptosis may provide a central pivot for disease production. Precipitating factors such as UV light, infections or drugs may cause increased apoptosis. Alternatively, they may induce dysfunctional clearance of apoptotic particles. This in turn results in increased exposure of the target antigens, and subsequent production of the corresponding autoantibodies. Conversely, reduced apoptosis has been implicated via a totally different mechanism.²³ Evidence suggests that some T cells from patients with lupus overexpress the oncogene bcl-2, promoting cell survival by decreasing apoptosis. This could potentially allow autoreactive T cells to persist, propagating the autoimmune response.

HORMONAL FACTORS

Sex hormones play an immunomodulatory role in the development of autoimmune disease. SLE, in particular,

predominantly affects women, with females commonly affected up to ten times more than males. Oestrogen is further implicated in the pathogenesis of lupus by the observation that SLE tends to affect women in the years between their menarche and menopause. Oestrogen can act as a potent disease stimulator in lupus-prone mice.²⁴ In addition, there is evidence from mouse models that androgens may be protective against the development of autoimmunity.²⁵ This observation has stimulated interest in the use of androgens as treatment for SLE.²⁶ There are conflicting data about the risk pregnancy poses to women with SLE, but many clinicians worry about the precipitation of flares. There is also anxiety regarding the use of exogenous oestrogens, both in the oral contraceptive pill and hormone replacement therapy. The literature is hampered by a lack of prospective data, but in a recent review, Mok and colleagues concluded that the use of exogenous oestrogens does carry a risk of disease exacerbation.²⁷ Moreover, in a group already at risk of thromboembolic disease, the use of hormonal treatments could be potentially harmful.

ENVIRONMENTAL FACTORS

Viruses

In the disease model that proposes SLE pathogenesis to be a combination of genetic susceptibility followed by exposure to an environmental trigger, viral infection provides a convenient putative target. Many possible culprits have been investigated.²⁸ Epstein-Barr virus (EBV) is among the most popular candidates but even here, the evidence is patchy. There are also case reports and studies looking at a variety of other viruses, including cytomegalovirus, parvovirus B19 and the retroviruses. To date, however, no overwhelming evidence favouring a particular pathogen has emerged.

Ultraviolet light

Photosensitivity is a common presenting symptom of SLE. Ultraviolet (UV) light exposure causes rash and even systemic flare in susceptible individuals. Some patients are highly sensitive to this effect, and one case report describes exacerbation of cutaneous lupus following exposure to UV light emitted from a photocopier!²⁹ Sontheimer reviewed proposed mechanisms for UV light induced lupus,³⁰ and the hypothesis is as follows. As previously mentioned, anti-Ro antibodies are particularly associated with the development of a photosensitive rash. UV light exposure causes the release of proinflammatory cytokines and increases the rate of keratinocyte apoptosis. In combination, this causes exposure of autoantigens including Ro, and subsequent keratinocyte cytotoxicity.

CONCLUSION

Much progress is being made in increasing our knowledge of the aetiopathogenesis of this complex disease. This understanding has brought with it the potential targeting of key molecules and the reasonable hope that this specificity will reduce the side effects associated with more general immunosuppression. Although the mortality associated with SLE has substantially reduced in the last decade, it remains a serious, potentially life-threatening condition, and careful long-term follow-up of patients with SLE remains paramount.

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