CELLULAR IMMUNOLOGICAL DYSFUNCTION IN SYSTEMIC LUPUS ERYTHEMATOSUS

Chee Yam Cheng

Department of Medicine III
Tan Tock Seng Hospital
Moulmein Road
Singapore 1130

Chee Yam Cheng, MBBS, MRCP(UK),
M. Med (Int Med)
Senior Registrar

SYNOPSIS

Normal people are known to possess autoreactive cell clones probably kept in check by immunoregulatory T helper and suppressor cells. Polyclonal B cell hyperreactivity in SLE could be triggered by a virus rather than be a sequel to deficiency of T suppressor cells, which, though well substantiated to exist in active SLE as a result of selective depletion by anti-T cell antibody, is felt to perpetuate the disease. Lymphocytotoxic antibodies generated against a possible viral agent could also lead to T suppressor cell dysfunction. Anti-T cell antibodies to various T cell subsets are part of the spectrum of auto-antibodies in SLE and appear responsible for the anergic state in active disease. Discoid LE patients have intact cellular immunity which breaks down if the disease is systemic.

INTRODUCTION

In systemic lupus erythematosus (SLE), humoral abnormalities related to B lymphocyte function in the production of autoantibodies are well documented. Less well known but by no means less important are the cellular immunological aberrations which have recently come into prominence. Immunoregulatory dysfunction is now thought to play a significant role either in the initiation and/or the perpetuation of the disease. This presentation reviews these aspects.

T and B lymphocytes: differentiation and enumeration

There are two kinds of lymphocytes: B cells and T cells. Each clone of B cells is genetically programmed to make a particular antibody with combining sites that recognise a particular epitope: a region of an antigen molecule with which the antibody interacts. In its resting state, a B lymphocyte displays some of its antibody as receptors on its surface. Contact of a receptor with its specific antigen stimulates the B cell to proliferate and differentiate forming a clone of antibody-producing plasma cells that manufacture millions of identical antibody molecules.

Whereas B lymphocytes mediate humoral immune mechanisms involving soluble antibodies, the T lymphocytes mediate cellular immunity. They too have specific receptors on their surfaces that recognise epitopes in antigen molecules. The recognition of an antigen prompts the release from the T cells of lymphokines, chemical substances that have multiple effects. Other T lymphocytes influence the production of antibody by B cells. One type, the helper cells, facilitates the proliferation of B cells for antibody production, and another type, the suppressor cells, retards it. In SLE, T cells seem to be important because their regulatory function is disturbed rather than because they damage tissue directly i.e. via delayed hypersensitivity reactions, graft versus host reactions or cell-mediated cytotoxicity.

To differentiate these different lymphocytes, surface receptors have proved useful. Lymphocytes have recognition units on their surface which can bind specific substances. Receptors for certain plant lectins can be used to identify classes of lymphocytes. For instance, phytohaemagglutinin (PHA) and conconavalin A (conA) react primarily with T cells whereas poke-weed mitogen stimulates both T and B lymphocytes. Lymphocytes also have a specific receptor for a site on the Fc portion of the IgG molecule. This Fc receptor thought initially to be a specific B cell marker, has been recognised on activated T cells and on lymphocytes devoid of characteristics of either T or B cells, i.e. 'null' cells. Individual classes of lymphocytes have unique receptors. For example, T lymphocytes bind heterologous erythrocytes to their surface. This specific interaction (E rosette formation) has proved useful in enumerating the T cells in a lymphocyte population. Sixty to 75% of normal human peripheral blood lymphocytes form spontaneous sheep erythrocyte rosettes suggesting a T cell origin. Fifteen to 25% show stainable surface immunoglobulin, usually accompanied by the presence of Fc and complement receptors, indicating a B cell origin. The remaining approximately 5 to 15% of cells without easily demonstrable surface receptors are called 'null' cells.

Problems in the enumeration of T and B lymphocytes in disease states must be appreciated. These are 1) some of the markers for T and B lymphocytes overlap. Both Fc and C3b receptors are present on a variety of the cells, notably "activated T cells", monocytes and macrophages; 2) many of the markers hold true only for normal lymphocytes and their stability in stimulated, abnormally differentiated or neoplastic lymphocytes is unknown. Even the surface phenotype of normally differentiating lymphocytes show considerable variation as they go from resting to activated forms; 3) many lymphocyte separation methods lead to a differential loss of one or another of the lymphocyte populations; 4) the blood lymphocyte pool is not necessarily representative of cells in the spleen or lymph node nor entirely representative of the total recirculating lymphocyte pool. Stress and other factors can alter lymphocyte trafficking and thereby produce abnormalities in distribution; 5) autoantibodies to T cells exist. These antibodies coat T cells and are detected as immunoglobulin-bearing cells falsely distinguishing them as B cells.

Newer techniques for distinguishing T and B cells and their subsets have evolved. It has been recently shown that human T cells which serve helper functions have a surface IgM receptor whereas T suppressors have an IgG receptor (1).

Autoreactive cell clones and their regulation

Burnet's concept of autoimmunity is that the emergence of a "forbidden clone" of B lymphocytes is the primary event in the production of autoantibodies (2). There exists in the body a heterogeneous population of antigen-binding cells which appear preset to proliferate into cells forming an antibody product or an immune response specific for the diverse antigens which a person will be presented with during his lifetime. It has been thought that in the foetus and perhaps early life,.exposure of autoantigens to these antigen-binding cells had resulted in the elimination of such cells so that no autoantibodies would be formed in later life unless a "forbidden clone" arose by mutation. Failure of "privileged" autoantigens, because of their sequestrated sites, like those in the brain or thyroid, for example, to be so exposed to these antigen-binding cells, was thought to result in autoantibodies being produced to these tissues when these antigens were released into the blood stream as a result of tissue injury in later years.

Inconsistent with the above theory is the detection of autoantigen-binding cells in the peripheral blood of normal subjects and patients with autoimmune disease (3). Studies were performed with thyroglobulin and native DNA (nDNA) and for both autoantigens, a low number of thyroglobulin-binding cells and nDNA-binding lymphocytes were present in normal people. In active SLE patients, increased numbers of nDNA-binding cells were found. These cells appeared to be B lymphocytes (4). Patients with inactive SLE had less of these cells than those with active disease but more than the normal controls. This suggested that SLE patients did not differ from normal simply because of the presence of a larger number of antigen-sensitive T lymphocytes that could enable a cooperative B-T lymphocyte anti-DNA response to occur. The presence of DNA-antigen binding cells in normal individuals presumably excludes the simple explanation that tolerance to nDNA is due to a lack of immunocompetent cells able to react with DNA. The binding of DNA to these B lymphocytes would initiate the production of antibodies to the DNA by these B lymphocytes which then transform into plasma cells. This antiDNA response could arise by one of three mechanisms: a) the emergence of a population of helper T cells b) the disappearance of a population of suppressor T lymphocytes, or c) another mechanism that bypasses the need for a helper T lymphocyte.

That normal people are capable of containing the potentially self-reactive proliferation of nDNA-binding cells reflects the presence of a control mechanism as suggested above. The body has surveillance mechanisms which may not periodically eliminate autoantigen-binding cells as was put forward in the concept of the forbidden clones (5). A B cell stimulant could trigger off the nDNA-binding B lymphocyte to

produce nDNA antibodies. Virus infection e.g. the Epstein-Barr virus (6), non-specific stimulators like mitogens or adjuvant e.g. endotoxin (7), could be responsible. The significance of virus-like particles in the tissues of SLE patients is unresolved (8). Once B cells overactively produce antibodies, some of which act on T cells to cause especially loss of their suppressor function, the unsuppressed B cells continue to be active. This circular concept would invoke roles for the T helper and suppressor cells.

T cell subsets in SLE

Active SLE is often accompanied by leukopenia (9). Enumeration of T and B lymphocytes in these patients has revealed decreased numbers of circulating T cells, recorded as a relative decrease in both the proportions and numbers of identifiable T cells as well as an apparent increase in certain B cell populations (10-13). The T cell peripheral cytopenia is thought not to reflect tissue sequestration within lesions (14) but a depletion of circulating T cells. This is most striking during active disease and is partially attributable to anti-T cell antibodies (anti-lymphocyte antibodies) which may deplete the body of T cells. Clinical correlations of these antibodies to the clinical course of SLE have been shown (15, 16). Further the T cell loss appears to be a selective one affecting T suppressor cells and not T helper cells, which are normal (10, 13, 17). Levels of null cells are elevated in SLE (10, 17, 18).

Recent studies of the cellular immune system in SLE have focussed on cellular cooperation and disordered regulation of the immune response. For T-dependent antigens, antibody induction requires the cooperation of T cells which perform a helper function for the B cells in question. Low doses of these antigens can make such T cells tolerant vitiating their helper function. Thus self-tolerance to potentially autoantigenic body components present in low concentrations in tissues is probably a T-cell based tolerance (19).

Evidence from mouse experiments show that T cells express suppressive effects which regulate both humoral and cellular immune responses (20) as well as helper functions. The suppressive effects are important in maintaining experimentally-induced tolerance to foreign antigens (21). Self-tolerance based solely on T cell tolerance is not infallible; it is by-passed by antigens in which the relevant determinant are coupled with a different carrier (22) but still, suppressor T lymphocytes must play an important role in maintaining self-tolerance. Talal (23) in reviewing studies on the animal model of SLE (mouse strain NZB and its related hybrid NZB/W), suggested that autoimmunity be viewed as a disorder of immune regulation so that decreased T suppressor cell activity or increased T cell helper activity sufficient to disturb the balance could lead to proliferation of B cell clones capable of autoantibody production.

In SLE, suppressor cell dysfunction has been shown to play a key role in the expansion and hyperactivity of the autoreactive clones (24-27). Suppressor cell dysfunction in active SLE is limited to the T cell subpopulation as shown by their failure to be activated by con A (27). Further this suppressor cell dysfunction is due to suppressor T cell antibody in sera of the patients (16). There is a strong quantitative correlation between the loss of suppressor T cell function and the activity of SLE as measured by the presence of antibodies to nDNA (17, 29). These workers and others (26) also found the serum of patients with active SLE to contain a soluble factor that induces a suppressor T cell defect in normal peripheral blood lymphocytes. The impaired suppressor activity in SLE patients thus resides in the generation of suppressor T cells, rather than in the response to suppressor T cell signals. Fauci et al (13) extended this work and showed a selective depletion of T suppressor cells in SLE. The "autologous mixed lymphocyte reaction", which occurs when autologous non-T-cells (B cells, monocytes and others) stimulate a proliferative response by T lymphocytes from the same donor, is deficient in SLE patients (30, 31). This reaction is specific and induces immunologic memory in the participating cells. Whether this means just a defect in the responding T cell alone or also in the stimulating non-T-cell is unknown. Further, patients with inactive SLE have a defect in the ability of T gamma cells (T suppressors) to respond to autologous non-T-cells and a reduction in numbers of such cells (13). This T gamma defect correlates with a loss of suppressor cell generation for the mixed lymphocyte reaction and is one of the few markers available for minimally active or inactive lupus erythematosus.

Anti-T cell antibodies and Lymphocytotoxic antibodies

Lymphocytotoxic antibodies (LCTA) were shown in the sera of SLE patients by several investigators (10, 16, 32, 33). Some of them were shown to be specific for T cells (16, 33) and a T cell subpopulation (10). This antibody was IgG according to some workers (28) but others (34) found it to be IgM. Both these classes of antibody selectively eliminated a population of T cells capable of developing suppressor function. The most common antilymphocyte antibody is a cold reactive, complement-dependent IgM lymphocytotoxin (32, 33, 35). Not all antilymphocyte antibodies are cytotoxic; some IgG blocking antibodies have been detected (33, 36, 37). Anti-T cell antibodies are more common than anti-B cell antibodies (10, 16, 33). Some antilymphocyte antibodies also react with monocytes and granulocytes (38).

It would seem that LCTA are heterogeneous, not only in their cytotoxicity or otherwise on the various lymphocytes (T, B or null) & their subsets, but also in their origination. They could result from unrestrained B cell autoantibody production as part of the generalised B cell hyperactivity in SLE or alternatively, reflect the operation of environmental factors in the aetiology of the disease.

Relatives of SLE probands have a higher incidence of LCTA, more than 50% versus 3% in controls, and close household contacts correlated much better with the presence of lymphocytotoxins than consanguinity (39). This suggested an important role for environmental pathogenic factors. There is evidence that viruses, particularly C-type viruses, are involved (40) and it is conceivable that selective infection with such a virus might functionally inhibit suppressor cells via

cross-reacting lymphocytotoxins.

Is B cell hyperreactivity secondary to T suppressor cell dysfunction?

Thus far, this review has shown that normal people have autoreactive cell clones with potential autoantibody production that are kept in check by a balance of T suppressor and helper cells. Viruses, as direct polyclonal B cell activators, or via the stimulation of LCTA production with anti-T suppressor cell effects, could lead to an explosive production of a range of autoantibodies, which include those with specific anti-T suppressor cell activity. The latter would enhance the proliferation of autoreactive B cells and their production of autoantibody to give autoimmune disease. Central to this hypothesis is the B cell hyperactivity. Are these B cells hyperactive because of a preceding suppressor cell defect or is the latter just an epiphenomenon that amplifies the chain of events leading to active SLE?

In active states of human SLE, there is suppressor cell dysfunction which is reversible and becomes normal when the disease remits (24). In the NZB/W mouse model of SLE, suppressor T cell deficiency was demonstrated early in life and became progressive during the short life span of the animals (41). This suppressor dysfunction seemed to precede the autoimmune state.

SLE is associated with excessive B cell activity that is generalised and not limited to the production of autoantibodies (42). These workers showed that such patients had increased numbers of IgM antibody-producing cells to defined chemical haptens and to sheep red blood cells only during active disease. The magnitude of this activity to a given hapten varied between individuals and may be genetically controlled. Based on these studies, there seemed to be at least three defects in B cell function during active SLE; a) increased synthesis of immunoglobulins b) increased numbers of immunoglobulin-synthesizing cells in the blood, and c) increased production of autoantibodies.

To further shed light on whether the suppressor T cell defect precedes the development of anti-T cell antibodies or vice versa, the proliferation response to pokeweed mitogen and spontaneous proliferation of lymphocytes were measured (10). Peripheral blood cells from patients with active, mildly active, inactive disease, and normal subjects responded equally well to the B cell mitogen pokeweed but patients with SLE had a tenfold increase in B cell proliferation without exogenous stimulation.

Therefore it seems that B cell abnormalities present in subtle form in patients with inactive disease become florid when the disease is active. Inactive lupus erythematosus B cells proliferate excessively without stimulation in culture suggesting an underlying B cell propensity to hyperactivity. That this hyperactivity is due to polyclonal B cell stimulation, e.g. by viruses, remains unproved.

Inactive lupus erythematosus patients may have a quantitative and functional defect in T gamma (suppressor) cells and increased B cell reproductive capacity and yet not manifest illness (43). Further insults especially polyclonal B cell stimulation, production of anti-T cell antibodies and loss of T cell regulatory function may be sufficient to turn inactive into active disease. T non-gamma cells must be functionally ineffective before florid autoantibody production occurs.

Gilliam and Hurd (44) studied circulating T and B lymphocytes in discoid and systemic lupus erythematosus patients. Discoid lupus erythematosus (DLE) is a disease which is almost always confined to the skin; autoantibody production with extracutaneous deposition of immune complexes rarely, if ever, occurs (45). Although most patients with DLE have disease that remains confined to the skin, a few have antinuclear antibodies (46), a small number develop extracutaneous disease (47) and approximately 15% of SLE patients have typical discoid skin lesions (46). DLE appears to fall within the LE spectrum (45) and as SLE patients have defective cellular immunity, a T cell function, and enhanced antibody formation, a measure of B cell function such defects perhaps in lesser degree may be expected in DLE. It was found that DLE patients had normal numbers of T cells but significantly increased numbers of B cells when compared with both the normals and the SLE patients. Further the SLE patients had significantly decreased numbers of T cells when compared with the DLE patients and with normals. These results suggested that cellular immunity is intact in DLE as the total number of T cells were similar to those of normal controls, while it is reduced in SLE. DLE may remain confined to the skin because T cell function in these patients is relatively normal with effective T cell suppression of autoantigen responsive B cells. Despite their normal T cell function, DLE patients have increased B cells but the absence of some additional stimulus, such as may be present in SLE, prevents these B cells from differentiating into autoantibody secreting plasma cells. Alternatively, it could be lack of anti-T cell (suppressor) antibody or LCTA in DLE that prevents it becoming a systemic disease. Immunogenetic aspects could throw light on this switchover from DLE to SLE.

Suggested factors in the pathogenesis of SLE

First there is genetic predisposition to excessive B cell activation. Second, genetic high responder status to immunisation with lymphocyte antigens or modified lymphocyte antigens, and with nuclear antigens exists. Third, stimulation with a polyclonal B cell activator or immunisation with modified lymphocyte membranes, (e.g. as a result of viral infection) or immunisation with endogenous or exogenous nuclear antigens, is necessary to initiate the disease (43). Further, male sex hormones tend to suppress and female hormones increase the immune response (48).

Expansion of B cell clones permitted by the high responder status to lymphocyte and nuclear antigens, would produce antibodies to these antigens; the anti-lymphocyte antibodies would help eliminate, initially, suppressor cells whose function is already strained by the polyclonal B cell activation. Later, helper cells are also destroyed. But B cell function would then be semi-autonomous. Hyperglobulinaemia, autoantibody production, disease production, impaired T cell

function and a continuing vicious cycle of B cell hyperactivity and regulatory T cell dysfunction result in active disease. Therapeutic intervention interrupts this cycle but the susceptibility to repeat this cycle of events remains and recurrence occurs as soon as drugs are tapered to a low enough level or a strong enough B cell stimulus is present. Any of a variety of infectious agents might serve as polyclonal B cell activators and also as stimuli for production of anti-lymphocyte and antinuclear antibodies (43).

Glucocorticoids and the T lymphocytes

In. vivo corticosteroid administration to normal subjects causes a selective depletion of T lymphocytes from the peripheral circulation with the absolute number of B cells decreasing to a lesser extent (49-51). Further, hydrocortisone-induced lymphopenia represents not a destruction of cells but a redirection of traffic of predominantly recirculating lymphocytes from the peripheral blood pool to other lymphocyte pools, particularly to the bone marrow (52, 53). The selective effect on T rather than B cells extends over to T cell subpopulations. Administration of hydrocortisone to normal subjects produced a selective depletion from the circulation of T helper cells and T cells with no detectable Fc receptor. The T suppressor cells were relatively resistant to the lymphopenic effect of hydrocortisone (54).

It thus seems possible that the selective depletion of a helper T cell subpopulation by corticosteroids with the resulting relative increase in proportion of suppressor T cell subpopulation contributes to the therapeutic effect of this drug in diseases associated with a lack of suppressive immunoregulatory control.

Cell-mediated Immunity

Numerous reports have now been accumulated regarding a general hyporeactivity or apparent depression of cell-mediated immune functions during the course of SLE (55-65). A decrease in the relative number of T lymphocytes (11, 12), abnormalities in the functional status of T lymphocytes (57, 62-65), and decreased delayed hypersensitivity reactions to common skin test antigens (55-58, 60, 62, 63) have been documented. However one report (66) which investigated cellular immune responses by skin testing, and mitogen-and antigen-induced transformation of peripheral blood lymphocytes implied that cellular immunity is normal in SLE.

The hyporeactivity to delayed skin tests correlated with disease activity, those with moderate to severe disease activity having significantly fewer positive responses than control subjects, and a higher frequency of anergy than either the control subjects or the patients with mild SLE (62, 67). Further, peripheral lymphocyte counts were significantly decreased inthe anergic SLE patients and in those with moderate to severe disease activity (67). The correlation found between skin test reactivity and absolute lymphocyte count suggests lymphocytopenia as the mechanism of the immune suppression. The most marked impairment of almost all parameters of cell-mediated immunity in patients with active SLE returned to near normal status when the disease was less active (63).

As indicated previously (9, 47), patients with discoid lesions are in fact at an early stage of SLE that may precede the appearance of systemic manifestations. This is supported by the finding that the DLE patients had cell-mediated immunity that did not differ significantly from control subjects. Patients with the overlap syndrome with hypocomplementaemia had a normal or a just minimally depressed cellular immune response (63).

It is not possible to know if the depressed cellular immunity in active SLE is secondary to a viral infection, as proved experimentally with measles virus (68) or predisposes the host to infection with an unknown aetiologic agent. Paty et al (62) also showed that patients with moderate to severe SLE had a significantly higher 7s antibody response than those with mild activity on testing the primary immune response to keyhole limpet hemocyanin. In view of the significant correlation of both the impaired cell-mediated responses and increased production of 7s antibody in response to primary immunisation with disease activity in SLE, this would suggest that the abnormal immune responses are more likely to be a secondary effect of the disease rather than a primary event in the pathogenesis of SLE (62).

CONCLUSIONS

In simplified terms, to summarise, B cell hyperreactivity in SLE is a polyclonal process resulting in various autoantibodies including those to native DNA. This polyclonal activation could be virus-triggered and results in lymphocytotoxic antibodies as well as anti-T cell antibodies that selectively deplete immunoregulatory suppressor T cell subsets in SLE. Whether the LCTA formed in response to virus infection, depletes T suppressor function leading to B cell hyperreactivity or the virus or other polyclonal B cell stimulators is/are responsible for B cell hyperreactivity leading to specific anti-T suppressor cell depletion remains unclear. However the depletion of T suppressor cells would result in the perpetuation of the autoimmune state (69). If it is accepted that DLE and SLE are part of the same disease spectrum varying only in the severity of immune dysfunction, then current evidence points to an intact T cell system with hyperactive B cells in the initial limited disease, going onto additional T cell dysfunction in the systemic disease.

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