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APOPTOSIS IN LUPUS PATHOGENESIS

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1. ABSTRACT

Apoptosis has been implicated in lupus pathogenesis in at least three different ways. As antigen, apoptotic material drives autoimmune responses. As immune modulator, impaired apoptosis makes patients susceptible to developing autoimmunity. As effector mechanism, apoptosis participates in target organ injury. This review summarizes the evidence that links apoptosis to these components of lupus pathogenesis.

2. INTRODUCTION

Apoptosis, the process of programmed cell death, has been linked to lupus pathogenesis. The relationship of apoptosis to lupus, however, cannot be fit into a simple platitude such as "lupus is a condition of inadequate apoptosis," or "lupus is a condition of excess apoptosis." Rather, roles for both "too much" and "too little" apoptosis have been found. Moreover, "too much" and "too little" apoptosis can occur at the same time in the same lupus patient. To understand the relationship(s) of apoptosis to lupus, this review will emphasize three features of lupus pathogenesis: a. lupus as an antigen-driven disease, b. lupus as a disease of excess autoimmunity, and c. lupus as a cause of end organ injury. Corresponding to these three features of lupus, at least three distinct roles for apoptosis have been described in lupus: a.) apoptosis as producer of autoantigen driving the initiation and progression of disease; b.) apoptosis as modulator of immune reactivity, with promotion of disease by impaired apoptosis; and c.) apoptosis as mechanism of disease-related target organ injury.

Before looking to the role of apoptosis in lupus, evidence to support the general premises that lupus is antigen driven, associated with dysregulated immunity, and a cause of tissue injury is briefly summarized below.

Lupus as an antigen-driven disease: The initial immunizing antigen(s) that drive the development of lupus are unknown, but characteristics of the immune response in lupus suggest that it is an antigen-driven condition. A number of phenomena have been observed after inoculation with known antigens that distinguish antigen-driven immune responses from other patterns of immune activation. These include oligoclonal expansion of antigen-specific cells (1), up-regulation of parallel B and T cell responses against the same antigen (2), epitope spreading to progressively more diversified structures on the antigen (3) and selection for immune cells with higher affinity for the antigen (4). In lupus, all of these phenomena have been identified. Oligoclonal expansion of antigen-specific cells has been observed in both lupus B cells and T cells (5,6). Patients with parallel B and T cell responses against lupus autoantigens have been reported (7). Epitope spreading of autoimmune responses from a limited initial response to a more diversified responses has been demonstrated in both human disease and animal models of lupus (8,9). Evidence of affinity maturation to lupus autoantigens also exists (10).

Lupus as a disease of excess autoimmunity: Lupus differs from other antigen-driven immune responses in several respects that suggest potential dysregulation of the immune response. Immunity in lupus is directed against self antigens not targeted in normal individuals, suggesting a failure of self-tolerance (11). Relatives of lupus patients and animal models of lupus show increased susceptibility to other autoimmune conditions in addition to

lupus (12). In animals engineered to have defective immune control mechanisms, development of lupus has been documented (13,14). Abnormalities in immune cell antigen recognition signaling have also been described in humans with lupus (15). Despite their enhanced autoimmune responses, lupus patients are at high risk for infection (16). Defects in host defense mechanisms as well as treatment-induced immunosuppression may lead to this risk (17). Certain infections, in turn, may contribute to dysregulation of immune cells.

Lupus as a cause of end organ injury: While lupus causes only transitory symptoms in some patients, it often leads to persistent end organ injury. Examples of persistent end organ pathology encountered in lupus include glomerulonephropathy (18), cutaneous injury (19), and sequelae of thrombosis (20). In neonatal lupus, damage to the developing heart has also been documented (21). A damage index in lupus has been developed and validated to measure the wide variety of forms of damage associated with lupus (22). Cohort studies using this metric unequivocally demonstrate increased damage in patients with lupus compared to controls.

Using these three pathogenic principles of lupus as a framework, ways in which "too much" and "too little" apoptosis can contribute to lupus pathogenesis become clear. If apoptotic material exceeds the body's ability to dispose of it through non-inflammatory pathways, it can act as an antigen to drive lupus. If insufficient apoptosis prevents the destruction of autoreactive immune cells, then excess autoimmunity can emerge. If, as a result of immune attack, many host cells are prompted to undergo apoptosis, end organ injury can result.

3. PHYSIOLOGY OF APOPTOSIS

At its simplest level, apoptosis can be thought of as a killing event preceded by an activation signal and followed by clearance of the cellular remains. Since abnormalities at each step of this process have been implicated as risk factors for lupus, it is relevant to review the physiology of the apoptotic process. If abnormalities exist at multiple steps, pathogenic features of "too much" and "too little" apoptosis can occur simultaneously.

A key step in apoptotic cell death is proteolysis by the caspase family of enzymes. These primarily cytoplasmic cysteine proteases are constitutively synthesized as pro-forms that require cleavage to become activated (23). In apoptosis, caspases cleave one another, inducing a self-amplifying proteolytic cascade (24). Caspases also cleave a number of other proteins with roles in cell structure, function, and repair (25). Cumulatively, the loss of function (and in some cases gain of function) of caspase-cleaved proteins leads to apoptotic cell death (26).

Three major apoptosis-inducing signals have been identified, any one of which can initiate the caspase proteolytic cascade. Intracellular stimuli leading to apoptosis converge at the mitochondria, where release of cytochrome C into the cytosol promotes the activation of caspase-9 (27). Extracellular stimuli leading to apoptosis converge at cell membrane receptor proteins, where ligand-binding causes adapter protein clustering on the cytoplasmic tails of the receptors, with subsequent activation of caspase-8 (28). Finally, extrinsic cytotoxic granules (produced by T cells and NK cells) deliver the enzyme granzyme B into target cells where it directly cleaves and activates caspases (29). Additional regulatory and counter-regulatory proteins exist that can modulate cellular sensitivity to these pro-apoptotic signals (30,31).

Under most circumstances, clearance of apoptotic cells occurs with remarkable rapidity (32), without eliciting an inflammatory response (33). It has been argued that the ability to facilitate efficient, non-immune clearance of cellular material is one of the fundamental benefits that multicellular organisms derive from apoptosis (34). Apoptotic cells are rapidly endocytosed by neighboring cells, as well as by tissue-infiltrating macrophages (35). Features of apoptotic morphology that promote rapid clearance include the display of cell surface markers on apoptotic cells that promote opsonization and engulfment. Some surface markers on apoptotic cells lead directly to binding by neighboring cells, including phosphatidylserine (36), CD50 (ICAM-3) (37), and carbohydrate moieties (38). Binding of apoptotic cells is also promoted by serum factors that preferentially coat apoptotic material, including proteins of the complement system (39), C-Reactive protein (40), thrombospondin (41), and beta-2-glycoprotein-1 (42).

4. APOPTOTIC MATERIAL AS AUTOANTIGEN

Definitive proof does not exist to demonstrate that apoptotic material drives autoimmune responses in lupus. However, an increasing body of evidence supporting this possibility has emerged since it was advanced by Casciola-Rosen and Rosen in 1994 (43).

Lupus autoantigens are heavily represented among the structures that are chemically modified in apoptosis, either through direct caspase proteolysis (44), or due to downstream apoptotic effects (45). If it is not first removed by noninflammatory processes (46), apoptotic material is capable of being presented by specialized antigen presenting cells to induce immune responses (47). Animals inoculated with apoptotic material develop lupus autoantibodies (48). Immune responses in lupus patients can be identified that specifically target the apoptotically modified form of a lupus autoantigen (49). Immunity to a protein modified in apoptosis often develops in lupus patients before immunity to other components of the same complex are observed (50).

The hypothesis that apoptotic material drives lupus autoimmunity also provides satisfying answers to a number of mysteries in lupus. For starters, it can account for some of the diversity of autoantigens targeted in the disease. In lupus, a single patient may have autoimmunity to antigens from the cell membrane, the cytosol, and the nucleus. In apoptosis, intracellular boundaries become disrupted and cells become shrunken (51). Thus, membrane, cytoplasmic, and nuclear antigens become

clustered in close physical proximity (43), increasing the likelihood of antigen spreading between them. Moreover, membrane, cytoplasmic, and nuclear antigens all undergo structural modifications in apoptosis (52).

Apoptosis leading to the production of lupus antigens can also explain the tendency for lupus to flare after viral infections or sun exposure. Both of these processes can lead to increased apoptosis (53,54). An increase in the amount of apoptotic antigen present may cross a concentration threshold beyond which an immune response is mounted. The development of classic "LE cells" in lupus is also explained by apoptotic material: these are granulocytes that have phagocytosed apoptotic debris (55). The specificity of LE cells for lupus may reflect the fact that lupus in particular is characterized by a deficit of clearance of apoptotic material through usual pathways.

Perhaps most tellingly, apoptosis provides a mechanism whereby complement deficiency states can act hierarchically as risk factors for lupus. Complement component proteins bind to apoptotic material and facilitate its clearance (56). The ability of individual complement proteins to promote clearance of apoptotic material corresponds to the risk for developing lupus in subjects deficient in these proteins (57). Development of glomerulonephritis in complement-deficient animals is associated with failure of clearance of apoptotic material in the kidney (58). As a general phenomenon, impaired clearance of apoptotic material has been observed in lupus patients (59). This series of observations suggests that lupus is likely to emerge when the ordinary pathways that lead to non-inflammatory clearance of apoptotic material fail. Under such circumstances, an opportunity exists for apoptotic material to be recognized by the immune system and thereby to initiate an autoimmune response.

On the other hand, a major question for the hypothesis that apoptotic material acts as an antigen driving lupus responses has emerged. Since apoptosis is a common occurrence, why shouldn't the immune system develop tolerance to the modified forms of antigens seen in apoptotic cells, preventing autoimmunity?

Multiple possible answers to this question have been proposed. First, development of tolerance is a leaky defense against autoimmunity. Failure to delete or anergize the complete population of autoreactive immune cells has been observed at both the B cell and T cell levels (60, 61). Thus, in some cases, a strongly pro-immune stimulus can induce autoimmunity to commonly encountered structures (62). Moreover, in the absence of rapid clearance and specific tolerogenic or anti-inflammatory signals, apoptotic material may be a favorable immunogen. The packaging of cellular contents in apoptotic blebs could promote the recognition of independent, multimeric antigens that are capable of breaking tolerance (63). Also, uptake of protein fragments in apoptotic blebs rather than discrete proteins by antigen presenting cells may preferentially direct antigen for presentation (64), and uptake of apoptotic material may initiate pro-immune signaling by mature dendritic cells (65).

Specific barriers to the development of tolerance toward apoptotic material may also exist. Under ordinary circumstances, tissue clearance of apoptotic material may be so efficient that the immune system seldom encounters it, and thus does not develop tolerance to it. In an *in vitro* system, macrophages were found to prevent immunity to apoptotic material by competing with dendritic cells for uptake of apoptotic blebs (66). The ability to tolerize against apoptotic antigens may also be tissue-specific, potentially regulating the tissue expression of lupus. Thus, while a subset of immature dendritic cells that traffic to the intestine have been shown to take up and induce tolerance to apoptotic material (67), inflammatory bowel disease in lupus is rarely described (68).

Alternatively, in order to avoid tolerance, the apoptotic cells that act as lupus autoantigens may undergo atypical forms of apoptosis that lead to the production of differently altered antigens. In this way, abnormal execution of apoptosis might promote lupus autoimmunity. For example, if caspase activation is blocked, granzyme B causes direct proteolysis of lupus autoantigens, producing different protein fragments from those ordinarily seen in apoptosis (69). One situation where caspase blockade may be observed clinically is with viral infection. A number of viruses have been found to express proteins that inhibit caspase-mediated apoptosis (70-72). Consistent with a role for granzyme B-induced protein fragments in autoimmunity, proteins that are susceptible to granzyme B cleavage have almost universally been described to be autoantigens in human disease (69). The promiscuity of granzyme B for cleavage of autoantigens can be viewed as both an argument in favor of this hypothesis and a challenge to it, though. Since autoantigens associated with other autoimmune conditions including scleroderma and polymyositis are cleaved by granzyme B as readily as lupus autoantigens, additional factors must explain why immunity to these other antigens does not appear to be equally likely in lupus.

Finally, a "multiple-hit" hypothesis has been proposed. Under this scheme, apoptotic material may act as a lupus antigen only when a defect in immunoregulation is present that prevents the usual expression of tolerance to apoptotic material. If a subject with defective immunoregulation is exposed to a sufficient concentration of apoptotic material in a pro-immune context, immunity to apoptotically modified lupus autoantigens could emerge. In some cases, the defect in immunoregulation might have a broad phenotype. If such an individual was exposed to different autoantigens in a pro-immune context, then an alternative autoimmune disorder could emerge. Such general defects in immunoregulation may explain the increased prevalence of other autoimmune conditions in lupus families. In other cases, forms of immune dysregulation may lead to loss of tolerance specifically to apoptotic antigens. A line of mice engineered to overexpress interferon-gamma in their epidermis has been that described that develops a lupus-like syndrome and that develops clusters of epidermal apoptotic cells (73). This may be an example of a case where a primarily immunologic abnormality (excess interferon-gamma

production) exposes a deficiency in the clearance of apoptotic material that leads to the development of lupus. Impairments in macrophage uptake of apoptotic material (such as with complement deficiency) could also be an example of a loss of apoptosis-specific tolerogenic factors, since macrophages secrete anti-inflammatory cytokines when they ingest apoptotic cells (46). Abnormal cytokine production by macrophages exposed to apoptotic material has also been observed in multiple murine models of lupus (74).

5. IMPAIRED APOPTOSIS AND LUPUS SUSCEPTIBILITY

Apoptosis plays a crucial role in the regulation of the immune system. Disruption in apoptotic pathways can prevent the deletion of autoreactive cells (75), and impair the resolution of ongoing inflammatory responses (76). Some such disruptions have been associated with increased risk for the development of lupus. Impaired apoptosis can be caused by deficiencies in endogenous pro-apoptotic mediators, over-expression of endogenous anti-apoptotic mediators, or by acquired factors.

The fact that deficient immune system apoptosis can be a risk factor for the development of lupus is easily reconciled with the idea that apoptotic material may be an important lupus autoantigen. The existence of some intact apoptotic pathway(s) are required for embryological development (77), and play physiological roles throughout life (78). Although specific pathways relevant to immune regulation may be impaired, other pathways leading to the production of apoptotic material continue to function. Such pathways could produce apoptotic material to serve as a lupus antigen.

Impaired signaling through the fas receptor was one of the first molecular defects to be correlated with impaired apoptosis, and is an intensively studied risk factor for the development of lupus. MRL mice with defective fas receptors (MRL/lpr) or with defective fas ligands (MRL/gld) develop a lupus-like syndrome with extremely high penetrance (79). Stem cell transfer studies in animals have shown that impaired fas signaling of immune system cells confers lupus susceptibility (80). Impaired fas signaling, though, is not sufficient to induce lupus. The penetrance of lupus is lower in non-MRL mouse strains onto which the lpr and gld mutations have been placed (79). Humans with impaired fas signaling have also been identified. These subjects have a high risk for development of autoimmune syndromes, but do not uniformly develop lupus (81). The human syndrome of impaired fas activity has been termed Autoimmune Lympho-Proliferative Syndrome (ALPS).

Other defects in immune system apoptosis have also been linked to lupus. A recently described circulating factor, BlyS (BAFF, TALL-1, THANK, zTNF-4), has been shown to dramatically increase susceptibility to lupus in animals when over-expressed (82). BlyS is also over-expressed in humans with lupus compared to controls (83). A function of BlyS is as a B cell-specific anti-apoptotic mediator (84). Thus, enhanced susceptibility to lupus caused by BlyS over-expression may be due to impaired B cell apoptosis. Estrogen inhibition of B cell apoptosis may also contribute to the increased prevalence of lupus in women (85). Impairment of T cell apoptosis has also been associated with risk for developing lupus. The sle3 gene, a susceptibility factor for murine lupus, has been found to inhibit T cell apoptosis in response to T cell receptor signaling (86). A polymorphism of a protein expressed on phagocytic cells and NK cells, the gammaRIII Fc receptor (CD16a), is also associated with lupus manifestations due to disrupted apoptosis. Patients at higher risk of lupus nephritis were homozygous for a receptor allele associated with decreased activation-induced (apoptotic) cell death (87). Even impairment in the granzyme B pathway, which appears to participate in “fratricide” downregulation of T and B cells (88), has been associated with an increased risk for development of lupus-like syndromes (89). In contrast, abnormalities in an apoptotic pathway without known roles in immune response regulation have not been linked to excess autoimmunity (90).

Impairments in some apoptotic signaling pathways that confer risk for autoimmunity may also account for faulty responses to microbial pathogens. Animals with defective fas signaling do not respond optimally to challenges with pathogens (91). Defects in TNF/TNF Receptor function have been implicated in impaired immune cell apoptosis (92), and lead to increased risk of infection (93). The impact of the TNF/TNF receptors on risk for development of autoimmune conditions is currently being assessed in clinical medical practice. With the advent of anti-TNF therapy as a treatment for rheumatoid arthritis and inflammatory bowel disease, cases where patients develop classic lupus autoantibodies have been described (94). Flares of the autoimmune condition multiple sclerosis after anti-TNF therapy have also been documented (95).

If abnormalities in immune cell apoptosis are permissive for infection, it is also noteworthy that infections may be permissive for the development of lupus. Microbial structures have been proposed to act directly as molecular mimics to self antigens to provoke autoimmunity (96). Additionally, viruses that have been provisionally linked to the development of lupus, including Epstein-Barr virus and adenovirus (97,98), have been documented to have anti-apoptotic activities on immune system cells (99,100). Infections with these agents could induce or exacerbate immune dysregulation contributing to the development of lupus. Furthermore, viruses that inhibit caspase-mediated apoptosis could also lead to the production of atypically modified apoptotic self antigens with enhanced immunogenicity, due, for example to Granzyme B cleavage.

6. APOPTOSIS IN LUPUS TARGET ORGAN INJURY

Mechanisms that contribute to tissue injury include induction of cell death, activation of host defense responses, and alterations in tissue physiology. Apoptosis plays a self-evident role in cell death, but can also lead to

other forms of target organ injury. Moreover, the number of ways that lupus can lead to apoptotic cell death is remarkably diverse.

Lupus skin disease, lupus nephritis, and the cardiomyopathy of neonatal lupus all have features of apoptosis-induced cell loss (101-103). When autoantibodies bind surface structures on target cells, lupus can induce apoptosis due to antibody dependent cell mediated cytotoxicity (ADCC) (104). In ADCC, effector cells identify immune complex formation on the surface of target cells, activating pro-apoptotic signaling via pathways including fas ligation and granzyme B mobilization (105). ADCC in lupus can result from direct antibody binding to its cognate antigen on the surface of a target cell (106), or by (potentially nonspecific) precipitation of circulating immune complexes in the vicinity of a target cell (107).

Also, lupus autoantibodies may be able to directly induce apoptosis in some cases. Anti-annexin V antibodies from lupus patients have a direct apoptotic effect on endothelial cells *in vitro* (108). Cell-penetrating antibodies have been described in lupus patients that translocate to the cytoplasm and nucleus of cells, where their effects may provoke apoptosis (109).

Even in cases where antibodies do not directly induce target cell apoptosis, their binding may increase the susceptibility of target tissues to apoptosis from other insults. Modulation of apoptotic regulatory molecules can occur in target cells in lupus patients through as yet uncharacterized mechanisms. The potentially pro-apoptotic mediator p53 has been observed to be upregulated in cutaneous lupus lesions (110), and in damaged glomeruli (111). Increased expression of fas ligand and increased susceptibility to fas-induced apoptosis has been observed in renal tubular cells exposed to pro-inflammatory cytokines (112). Some of these effects may account for the increased apoptosis observed in antibody-bound keratinocytes exposed to UV light (113). Additionally, lupus autoantibodies bound to apoptotic fetal heart cells induce macrophage secretion of TNF-alpha, another potentially pro-apoptotic mediator (114). In addition to various mechanisms of antibody-mediated apoptosis, direct T cell-mediated cytotoxicity also appears to occur in lupus. In animal models of lupus where antibody secretion cannot occur, cellular cytotoxicity can still be observed (115).

Induction of a more intense inflammatory response is an example of how apoptotic material can mediate tissue injury by activating host response mechanisms. Experimentally, peripheral blood mononuclear cells have been observed to respond to the combination of apoptotic material and lupus IgG with production of interferon-alpha (116). If apoptotic material functions as a lupus antigen, induction of apoptosis in target tissue may also cause a self-amplifying immune response. If it is not efficiently cleared, the apoptotic material may be recognized by additional immune effector cells, potentially leading to further apoptosis of surrounding cells.

Induction of thrombosis is an example of how apoptosis can cause altered tissue physiology. If released into the circulation, apoptotic material is procoagulant (117). If apoptotic material is not rapidly cleared from circulation, it can therefore increase the risk of vascular thrombosis. If a thrombotic event occludes an artery, downstream ischemia causing both tissue necrosis and apoptosis can ensue. Also, some lupus antibodies appear to arise in response to apoptotically modified membrane phospholipids (117, 118). Lupus autoantibodies to phospholipid-associated antigens can induce endothelial cell apoptosis (108). Endothelial cell apoptosis itself is a procoagulant event (119). An accelerating spiral of increased apoptosis leading to increased thrombosis, in turn leading to increased apoptosis is a model that may account for cases of catastrophic lupus-associated thrombosis (120).

7. PERSPECTIVE

Abnormalities at many points in the process of apoptosis may be related to lupus pathogenesis. Abnormal execution of target cell apoptosis or impaired clearance of apoptotic material may lead to immune recognition of lupus autoantigens. Impaired activation of apoptosis in any of a variety of immune cell types may cause enhanced susceptibility to lupus autoimmunity. Excess activation of target cell apoptosis or impaired clearance of apoptotic material may lead to target organ injury.

On the other hand, abnormalities of apoptosis need not be present in all cases of lupus. While half of a group of patients with immunity to the lupus autoantigen U1-70kD were found to target apoptosis-specific epitopes on U1-70kD, the other half of the patients did not (49). Non-apoptotic forms of lupus autoantigens have been shown to be capable of inducing autoimmune responses (121), and promoting clinical manifestations of lupus (9). Abnormalities in immune regulation other than direct impairments in immune cell apoptosis also have pathogenic significance for lupus (122). Even lupus target organ injury can occur in ways that do not appear to involve apoptosis, such as in membranous nephropathy (123).

If addressing apoptosis in lupus pathogenesis is to succeed as a therapeutic strategy, the first challenge will be to identify the patient subsets in whom apoptosis is relevant. This may involve viewing lupus as a syndrome that demands a more precise disease to be diagnosed. In the future, clinicians may seek to make a diagnosis of AFAAD (Apoptotic Fragment-Associated Autoimmune Disease), VILS (Virally-Induced Lupus-like Syndrome), or ALSIT (Autoimmune Lupus-like Syndrome of Impaired Tolerance) in order to better treat their cohorts of lupus patients. In some subjects, more than one of these diagnoses may apply. Additional research will be necessary to define the extent to which abnormal apoptosis plays a role in the pathogenesis of individual cases of lupus.

This review article has highlighted three roles for apoptosis in the pathogenesis of lupus: apoptotic material as a source of lupus autoantigen, impaired immune cell

apoptosis as a cause of immune dysregulation, and tissue-specific apoptosis as a mechanism of lupus target organ injury. Improved understanding of how these factors contribute to the expression of lupus may contribute to more successful management of this condition.

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