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Review Article

Cellular Immunity in Autoimmune Disorders

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Abstract

This paper has reviewed many areas of cellular immunity in three important autoimmune diseases, systemic sclerosis, rheumatoid arthritis and systemic lupus erythematosus. It evaluated clinical and pathologic manifestations of systemic sclerosis, abnormal T cell immunoregulation, CD4 cells sensitized to human type I collagen. It also discussed, increased levels of IL-2, fibroblast-like synoviocytes in the pathogenesis of rheumatoid arthritis and mast cell mediators and, anti-IL-4 that might effect lymphocyte proliferation in patients with rheumatoid arthritis. IL-17 and Th17 cells, and CD4+ cells are key players in the development of rheumatoid arthritis and anti-IL-17 therapies might have beneficial effects. Systemic lupus erythematosus and the role of inflammatory mediators relevant to the pathogenesis of accelerated atherosclerosis was reviewed along with lupus nephritis, associated with higher mean carotid intima media thickness that can be a novel cardiovascular risk factor in premature coronary atherosclerosis. A link between allergic rhinitis, asthma, SLE was also reviewed.

Keywords: Rheumatoid arthritis; Interleukins; CD4+ T cells; Regulatory T cells; Systemic lupus erythematosus; Lupus nephritis

Scleroderma or Systemic Sclerosis

Systemic scleroderma or systemic sclerosis is one of the most complex systemic autoimmune diseases. It targets the vasculature, connective tissue-producing cells, such as fibroblasts/myofibroblasts and components of the innate and adaptive immune systems. Clinical and pathologic manifestations of systemic sclerosis are the result of: (1) innate/adaptive immune system abnormalities leading to production of autoantibodies and cell-mediated autoimmunity, (2) microvascular endothelial cell/small vessel fibroproliferative vasculopathy, and (3) fibroblast dysfunction generating excessive accumulation of collagen and other matrix components in the skin and internal organs [1]. All three of these processes interact and affect each other. The disease is heterogeneous in its clinical presentation and reflects different genetic or triggering factors such as infection or environmental toxins, influences on the immune system, vasculature, and connective tissue cells. The roles played by other ubiquitous molecular entities (such as lysophospholipids, endocannabinoids, and their diverse receptors and vitamin D) in influencing the immune system, vasculature, and connective tissue cells are just beginning to be realized and studied and may provide insights into new therapeutic approaches to treat systemic sclerosis [1].

Scleroderma (Progressive Systemic Sclerosis [PSS]) is known to be associated with abnormal T cell immunoregulation [2]. In this early study these authors evaluated lymphocyte phenotypes in patients with PSS and normal controls by flow cytometry and monoclonal antibodies for total T (CD3), T suppressor (CD8), T helper (CD4), T helper-inducer (CDw29), T suppressor-inducer (CD45R), human leukocyte antigen, DR+B (CD19), DR+T, and natural killer subsets, HNK-1 (CD57) and NKH-1 (CD56) cells [2]. Patients with PSS compared to normal subjects had significantly lower percentages of CD3+ and CD8+ cells similar to several patients with rheumatoid arthritis The study also evaluated) CD45R T+DR+ cells and NKH-1 (CD56) cells. Patients with PSS with late-limited or generalized disease had lower percentages of CD8+, CD19, NKH-1+, and CDw29, but higher percentages of CD4+, HNK-1, and CD45R cells compared to patients with early stage disease. These unique alterations in patients with PSS may prove to be useful in monitoring the stage of disease activity for therapy and further define immunologic defects [2].

In another early study, peripheral blood mononuclear cells (PBMC) from patients with systemic sclerosis produced increased amounts of interleukin-2 (IL-2), in a dose-

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dependent manner, in response to stimulation with human type I collagen, whereas PBMC from normal subjects did not [3]. At a dose of 50 micrograms human type I collagen PBMC from systemic sclerosis patients produced 8 times as much IL-2 as did PBMC from 16 normal subjects. And 3 times as much as did PBMC from a group of 13 rheumatoid arthritis patients. In contrast, IL-2 production by PBMC after nonspecific stimulation with the mitogen, phytohemagglutinin, did not differ among the systemic sclerosis, rheumatoid arthritis, and normal control groups [3].

Cell depletion experiments indicated that the IL-2-producing cells in systemic sclerosis patients are CD4+. Thus, systemic sclerosis patients have CD4 cells that are specifically sensitized to human type I collagen and can produce increased levels of IL-2. Measurement of IL-2 production stimulated by human type I collagen may be useful in evaluating disease activity, and further investigation of this process may contribute to the delineation of the pathogenesis of systemic sclerosis [3].

Rheumatoid Arthritis

Rheumatoid arthritis is a systemic autoimmune inflammatory disorder affecting the peripheral joints. The exact pathogenesis of rheumatoid arthritis remains is unclear, although strong evidence suggests the involvement of cytokines are important in disease progression since cytokines play a fundamental role in various inflammatory processes, articular destruction, and rheumatoid arthritis -associated comorbidities. It has been reported that IL-17 and Th17 cells play important roles in the pathogenesis of RA [4,5].

Fibroblast-like synoviocytes (FLS) play an important role in the pathogenesis of rheumatoid arthritis through aggressive proliferation, invasion, and certain proinflammatory cytokines that may affect synoviocyte proliferation [6]. To evaluate whether interleukin-21 (IL-21) could promote proliferation and proinflammatory cytokine production by rheumatoid arthrtis-FLS, These authors performed immunohistochemistry and immunoblotting and observed the expression of the IL-21 receptor (IL-21R) in synovial tissues and FLS from rheumatoid arthritis and osteoarthritis patients [7]. The concentrations of IL-6 and tumor necrosis factor-α (TNF-α) in culture supernatants were determined by ELISA. The signaling pathways triggered by IL-21 were then characterized by immunoblotting. IL-21R was upregulated in the synovial tissues and FLS of rheumatoid arthritis patients as compared with osteoarthritis patients. IL-21 stimulated rheumatoid arthritis-FLS proliferation and promoted the production of TNF-α and IL-6, and blockade of IL-21/IL-21R pathway with IL-21 rheumatoid arthritis Fc attenuated IL-21-induced proliferation and secretion of TNF-α and IL-6. IL-21 induced activation of the ERK1/2, PI3K/AKT and STAT3 pathways, and blockade of these pathways attenuated IL-21-induced proliferation and secretion of TNF-α and IL-6. These results suggested that IL-21 could promote rheumatoid arthritis-FLS proliferation production of proinflammatory cytokines and, therapeutic strategies targeting Thus, IL-21 might be effective for the treatment of rheumatoid arthritis [7]. Mast cell synovial hyperplasia can occur in patients with rheumatoid arthritis. Histamine can accelerate synovitis and heparin can inhibit lymphocyte function. Since Interleukin-4 (IL-4) can stimulate murine mast cell and IgE synthesis, These authors determined whether mast cell mediators and anti-IL-4 might affect lymphocyte proliferation from patients with rheumatoid arthritis [8]. Twenty-four patients with rheumatoid arthritis and nine normal controls were evaluated by history, physical examination, physician and patient-assessed joint, allergic symptoms, and diary scores. An IL-2-driven-T cell (3H) Tdr proliferation assay with monoclonal anti-IL-4 and a sensitive ELISA were performed with isolated peripheral blood mononuclear cells with either concanavalin A, type I human collagen, or heparin and histamine. Increased lymphocyte proliferation indices with Con A occurred in peripheral blood mononuclear cells from all patients with rheumatoid arthritis compared with normal controls which was inhibited in 32% of peripheral blood mononuclear cells by anti-IL-4 and increased IL-4 ELISA levels in cultured supernatants were noted with heparin and collagen [8].

Rheumatoid arthritis is characterized by persistent joint inflammation leading to breakdown of articular cartilage and bone damage [9]. Although the exact disease etiology is not known yet, it has been reported that rheumatoid arthritis arises from the breakdown of immune tolerance. The autoreactive T cell (CD4+ T cell) and impaired regulatory T cell (Treg) play an important role in the pathogenesis of rheumatoid arthritis T cells infiltrate into the synovial joint, and increase the level of pro-inflammatory cytokines (interferon-γ and IL-17), causing synovial cartilage and bone destruction [10].

Rheumatoid arthritis is one of the most common autoimmune disorders characterized by the chronic and progressive inflammation of various organs, most notably the synovia of joints, leading to joint destruction, a shorter life expectancy, and reduced quality of life [11]. There is substantial information about the pathophysiology of the disease with various groups of immune cells and soluble mediators identified to participate in the pathogenesis [11]. Therapeutic trials aiming to suppress IL-17 might provide some new treatments supplementing or replacing current existing biological therapies in rheumatoid arthritis [11].

Synovitis in rheumatoid arthritis is characterized by massive cellular infiltration of the synovium consisting mainly of leukocytes such as T and B cells, macrophages, granulocytes, and dendritic cells together with the increased local production of proinflammatory cytokines and chemokines, eventually leading to the destruction of the joint and bone [11]. T cells, especially CD4+ T cells, play a major role in this process, also supported by the effective use of Abatacept in the treatment of rheumatoid arthritis an agent that selectively blocks T cell costimulation [12]. However, following the description and characterization of IL-17 and Th17 cells, more and more data indicated that these latter types of CD4+ cells are key players in the development of rheumatoid arthritis and that anti-IL-17 therapies might have beneficial effects [13]. Th17 cells are a subgroup of helper T cells with the capability to produce high levels of IL-17.

This study confirmed that circulating fibrocytes are expanded in rheumatoid arthritis and that there is a direct correlation between the increase in the number of activated fibrocytes and increased number of CD4+ T cells. These authors suggested that interactions between circulating fibrocytes and activated T cells may promote disease activity and provide in vitro evidence that mouse-derived CD4+ T cells produce GM-CSF, which induces fibrocyte proliferation and, activated fibrocytes produce IL-6, promoting Th17 polarization [14].

Systemic Lupus Erythematosus

In Systemic Lupus Erythematosus (SLE) patients, the role of inflammatory mediators is relevant to the pathogenesis of accelerated atherosclerosis. CD40 ligand is increased in circulating lymphocytes, which correlates with double-stranded DNA, and has an important role in predicting risk of cardiovascular disease [15]. Vascular endothelial growth factor is a tightly regulated angiogenic cytokine in the kidney, and plasma levels have been associated with disease activity. It has been correlated with lupus nephritis, associated with higher mean carotid intima media thickness, and can be a novel cardiovascular risk factor in premature coronary atherosclerosis [15].

SLE may include a variety of disease entities, such as isolated cutaneous lupus, undifferentiated connective tissue disease, mixed connective tissue disease, and drug-induced lupus. There are many ongoing clinical trials in SLE patients of therapeutics with different mechanisms of cellular action, such as classic immunosuppression, cell depletion, antigen-specific immunomodulation, and targeting of antigen-nonspecific, immune-activating molecules [16]. New immune cell-targeted therapies are now available that are specifically designed to block cellular pathways involved in disease pathogenesis. Author stated the practicing physician should understand the immunology, pathogenesis, laboratory evaluation, and updated treatment options when diagnosing SLE in their clinic or daily practice [16].

Lupus Nephritis

In SLE patients, DNA fragments isolated from plasma may mimic microbial DNA and trigger Toll-Like Receptor 9 (TLR9) signaling with the formation of autoantibodies against DNA fragments and nucleosomes [17]. Vascular Endothelial Growth Factor (VEGF) is a tightly regulated angiogenic cytokine in the kidney. This study investigated glomerular and tubular expression of both TLR9 and VEGF in biopsies from human subjects with Lupus Nephritis (LN) and normal controls. Kidney biopsies in LN and normal controls were evaluated for expression of TLR9 and VEGF. The degree of kidney damage was analyzed according to the International Society of Nephrology / Renal Pathology Society classification. Immunohistochemistry was performed, and slides were incubated with antibodies against VEGF and TLR9 monoclonal antibody, stained with hematoxylin and eosin, and scored. Intense staining of glomeruli and tubules for TLR9 up to 3+ from patients with LN were observed. Samples from LN subjects showed 3+ staining of glomeruli but only up to 2+ in tubules for VEGF. There was less significant staining for TLR9 and none for VEGF in controls [17]. There was no correlation observed between LN class severity and intensity of staining for VEGF or TLR9. This is the first study that investigated combined expression of TLR9 and VEGF, which could be an important tool for understanding the role of TLR9 and VEGF in LN, with insights into the early detection and targeted treatment of this disease [17].

Physicians in practice should be knowledgeable regarding several aspects of autoimmune disorders, especially systemic lupus erythematosus and lupus nephritis. These disorders can present to the clinician's clinic and private office regardless of their specialty. This review discussed various aspects of SLE, its mechanisms of disease, role of accelerated atherosclerosis, proinflammatory cytokines, and therapeutic approaches. The role of vascular endothelial growth factor in which and plasma levels have been associated with disease activity, classification of severity, and diagnosis of lupus nephritis was addressed. Current treatment options, prognosis, and future therapeutic approaches and common side effects were also discussed [18].

This paper reviews the link between NF-κB and SLE, including B-cell development, signaling and cytokines, which play a crucial role in the pathogenesis of SLE and T-cell development, a key player in T-cell activation [19]. The roles of dendritic cells, which can promote tolerance or immunity to antigens, of polymorphisms and of NF-κB, which are linked with SLE, were also discussed. The role of Toll-like receptors, which are important in the pathogenesis of SLE and lupus nephritis was also discussed [19].

Lupus nephritis is a major complication of SLE that can lead to significant illness or even death without proper intervention and treatment. With vast implications through a novel mechanism, belimumab offers a new standard of treatment for physicians in the complications associated with SLE, specifically lupus nephritis [20]. By targeting B cell signaling and maturation, belimumab is able to mitigate the underlying pathological complications surrounding SLE. Phase 3 clinical trials with belimumab have depicted clinical efficacious applications, suggesting belimumab as a revolutionary breakthrough in the treatment armamentarium for practicing clinicians [20]. This article explained the precise mechanism of action of belimumab on the soluble protein BlyS that plays a major role in the pathogenesis of lupus nephritis. In addition, the extensive pharmacokinetics and clinical implications are exemplified in this review with belimumab's comparison with standard therapeutic guidelines for the treatment of lupus nephritis [20].

The purpose of this manuscript is to extensively review the literature related to systemic lupus erythematosus and atherosclerosis [21]. The conclusion of this review has covered accelerated atherosclerosis in systemic lupus erythematosus, the role of complement, interferon in premature atherosclerosis, inflammatory mediators such as cytokines, leukocytes, innate and adaptive immunity, hydrolytic enzymes, reactive oxygen species, vascular endothelial growth factor, toll receptors in lupus nephritis, several specific anti-inflammatory pharmacological therapies, and potential prevention strategies for atherothrombotic events, interferons and the inflammasome. It is important for allergist-immunologists, rheumatologists both in academic institutions and in practice to understand this important disorder [21].

SLE is associated with significant cardiovascular morbidity and mortality. Studies have established that patients with SLE develop accelerated atherosclerosis related to endothelial cell dysfunction and acute vascular events not explained by Framingham risk score risk stratification [22]. In this article, the authors closely explored the role of interferons in endothelial cell apoptosis and vascular dysfunction. Understanding the mechanisms responsible for the significant increase in atherosclerotic cardiovascular complications in patients with SLE, and the role of type I interferon may serve as the basis for developing target therapy with pharmacological agents [22].

This review discussed a link between allergic rhinitis, asthma, SLE and a case report in this area. A clear link with symptoms of allergic rhinitis, asthma and SLE exists. Several articles found

on Pubmed in the literature are listed on allergic rhinitis and allergy, Th1-immune responses, mast cells in autoimmunity, total immunoglobulin E levels in lupus, atopic diseases and SLE were reviewed [23]. In addition, risks and correlations, genetic predisposition, environmental factors, immune regulation, elevated serum IgE levels, regulatory B cells for both allergic and autoimmune diseases were mentioned, The role of asthma, allergy and autoimmunity, neutrophils, innate, adaptive immunity in the development of SLE was also covered in this referenced paper, along with the (Tim) gene family, compliment related to SLE, immunomodulation and hypersensitivity reactions in autoimmunity [23].

Conclusion

This paper reviewed many areas of cellular immunity in three important autoimmune diseases, systemic sclerosis, rheumatoid arthritis and SLE. It evaluated clinical and pathologic manifestations of systemic sclerosis, abnormal T cell immunoregulation, CD4 cells sensitized to human type I collagen. It also discussed, increased levels of IL-2, fibroblast-like synoviocytes in the pathogenesis of rheumatoid arthritis and mast cell mediators and, anti-IL-4 that might affect lymphocyte proliferation in patients with rheumatoid arthritis. IL-17 and Th17 cells, and CD4+ cells are key players in the development of rheumatoid arthritis and anti-IL-17 therapies might have beneficial effects. SLE and the role of inflammatory mediators relevant to the pathogenesis of accelerated atherosclerosis was reviewed along with lupus nephritis, associated with higher mean carotid intima media thickness that can be a novel cardiovascular risk factor in premature coronary atherosclerosis. A link between allergic rhinitis, asthma, SLE was also reviewed.

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