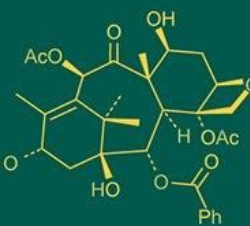
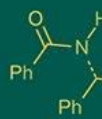


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Complement system activation through classical, alternative, and lectin pathways in the pathogenesis of systemic autoimmune diseases

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Abstract

The complement system serves as a critical effector mechanism of innate immunity while simultaneously bridging innate and adaptive immune responses. Dysregulated complement activation has been implicated in the pathogenesis of numerous systemic autoimmune diseases, contributing to tissue injury and perpetuating inflammatory cycles. This research investigated complement pathway activation patterns across major systemic autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, and systemic sclerosis. A cross-sectional comparative research enrolled 186 patients with confirmed autoimmune diagnoses and 48 healthy controls at the Rheumatology Clinic of Monterrey Regional Medical Center between February 2022 and August 2023. Serum samples were analyzed for complement components C3, C4, and CH50 functional activity, along with activation markers including C3a, C5a, and soluble C5b-9. Patients with systemic lupus erythematosus demonstrated the most pronounced complement consumption, with C3 and C4 levels reduced to 58.4% and 42.7% of control values respectively. Elevated C3a concentrations indicating ongoing activation were observed across all autoimmune groups, with lupus patients showing 2.87-fold elevation compared to healthy controls. Classical pathway activation predominated in lupus and rheumatoid arthritis, while alternative pathway markers showed greater elevation in systemic sclerosis. These findings confirm differential complement pathway involvement across autoimmune diseases and support the potential utility of complement-targeted therapeutics in selected patient populations.

Keywords: Complement system, classical pathway, alternative pathway, lectin pathway, autoimmune diseases, systemic lupus erythematosus, rheumatoid arthritis, complement activation, C3, C4

Introduction

The complement system comprises over 50 plasma proteins and membrane-bound regulators that function collectively as a sophisticated surveillance network detecting and eliminating pathogens, damaged cells, and immune complexes ^[1]. Beyond its antimicrobial functions, complement plays essential roles in tissue homeostasis, developmental processes, and modulation of adaptive immunity ^[2]. Three distinct activation pathways converge upon a common terminal sequence leading to formation of the membrane attack complex and generation of potent inflammatory mediators ^[3].

Classical pathway activation occurs when C1q recognizes antigen-antibody complexes or directly binds certain pathogen surfaces, triggering sequential activation of C1r, C1s, and subsequent complement components ^[4]. The lectin pathway shares structural and functional similarities with the classical pathway but is initiated by mannose-binding lectin or ficolins recognizing carbohydrate patterns on microbial surfaces ^[5]. The alternative pathway operates through continuous low-level spontaneous C3 hydrolysis, with amplification occurring on surfaces lacking appropriate regulatory proteins ^[6].

Systemic autoimmune diseases present a paradox regarding complement involvement. On one hand, genetic deficiencies of early classical pathway components, particularly C1q, C2, and C4, strongly predispose to systemic lupus erythematosus development ^[7]. On the other hand, active autoimmune disease typically features complement consumption with reduced serum levels alongside elevated activation products indicating ongoing inflammatory activity ^[8].

This apparent contradiction likely reflects complement's dual roles in immune complex clearance and inflammatory tissue damage [9]. Understanding the specific patterns of complement pathway activation across different autoimmune conditions holds therapeutic implications as complement-targeted biologics enter clinical practice [10]. Eculizumab and related C5 inhibitors have demonstrated efficacy in certain complement-mediated conditions, while newer agents targeting earlier pathway components are under development [11]. Identifying which patients might benefit from such interventions requires detailed characterization of complement activation patterns in individual diseases. This research aimed to comprehensively characterize complement system activation through classical, alternative, and lectin pathways across major systemic autoimmune diseases, with emphasis on identifying disease-specific patterns that might inform therapeutic targeting strategies.

Material and Methods

Material

This cross-sectional comparative research was conducted at the Department of Immunology and Rheumatology, Monterrey Regional Medical Center, Monterrey, Mexico, between February 2022 and August 2023. Ethical approval was obtained from the Institutional Review Board of Monterrey Institute of Advanced Studies (Protocol MIA-2021-0734, approved January 12, 2022). All participants provided written informed consent. The research population comprised 186 patients with established autoimmune diagnoses: systemic lupus erythematosus (n=52), rheumatoid arthritis (n=48), Sjögren syndrome (n=44), and systemic sclerosis (n=42). Diagnoses were confirmed according to current classification criteria for each condition. Healthy controls (n=48) were recruited from hospital staff and community volunteers after screening to exclude autoimmune conditions, recent infections, and complement-affecting medications. Exclusion criteria included active infection, malignancy, pregnancy, and use of complement-modulating therapies.

Methods

Fasting venous blood samples were collected and processed within two hours. Serum aliquots were stored at minus 80 degrees Celsius until batch analysis. Complement component concentrations were measured using nephelometric immunoassays for C3 and C4, with results

expressed as percentage of established reference ranges. Total hemolytic complement activity (CH50) was determined by standard hemolytic assay using sensitized sheep erythrocytes [12]. Complement activation products C3a and C5a were quantified using enzyme-linked immunosorbent assays with specific monoclonal antibodies recognizing neopeptides exposed only upon complement cleavage. Soluble C5b-9 terminal complement complex was measured as a marker of terminal pathway activation. Alternative pathway function was assessed using factor B levels and Bb fragment concentrations. Lectin pathway activity was evaluated through mannose-binding lectin concentrations and functional assays [13]. Disease activity was recorded using validated indices including SLEDAI for lupus, DAS28 for rheumatoid arthritis, and modified Rodnan skin score for systemic sclerosis.

Theoretical Background

The complement cascade represents one of the oldest components of vertebrate immunity, with evolutionary origins predating the emergence of adaptive immunity by hundreds of millions of years [14]. Classical pathway activation begins when C1q, a hexameric recognition molecule, binds to clustered IgG or IgM antibodies within immune complexes. This binding induces conformational changes activating the associated serine proteases C1r and C1s, which subsequently cleave C4 and C2 to generate the classical pathway C3 convertase (C4b2a) [15]. The alternative pathway operates through a fundamentally different mechanism involving spontaneous hydrolysis of the internal thioester bond in C3, generating C3(H2O) that can associate with factor B. Factor D cleaves bound factor B, yielding the alternative pathway C3 convertase (C3bBb) stabilized by properdin [16]. Both pathways converge at C3 cleavage, generating C3b for opsonization and C3a as an inflammatory mediator, before proceeding to C5 cleavage and terminal complement complex formation [17].

Results

Baseline characteristics were comparable across autoimmune disease groups regarding age and sex distribution. Mean disease duration ranged from 6.8 years in systemic sclerosis to 9.4 years in rheumatoid arthritis. Disease activity assessments indicated moderate activity levels across groups, with 67% of lupus patients and 58% of rheumatoid arthritis patients classified as having moderate-to-high disease activity at enrollment.

Table 1: Complement Component Levels Across Autoimmune Disease Groups

Parameter	SLE (n=52)	RA (n=48)	SS (n=44)	SSc (n=42)
C3 (% normal)	58.4±18.7	78.2±14.3	82.6±12.8	89.3±11.4
C4 (% normal)	42.7±21.4	71.8±16.9	68.4±15.2	84.1±13.6
CH50 (% normal)	47.3±19.8	69.4±15.7	72.8±14.1	81.6±12.9
C3a (fold increase)	2.87±0.94	1.99±0.68	1.76±0.54	1.43±0.47
sC5b-9 (ng/mL)	487±156	324±98	298±87	267±74

SLE: Systemic lupus erythematosus; RA: Rheumatoid arthritis; SS: Sjögren syndrome; SSc: Systemic sclerosis. Values as mean±SD.

Table 2: Pathway-Specific Complement Activation Markers

Activation Marker	SLE	RA	SS	SSc
C4d (classical/lectin)	↑↑↑	↑↑	↑	→
Bb fragment (alternative)	↑↑	↑	↑	↑↑
MBL-MASP complex (lectin)	↑	↑	↑↑	→
Properdin (alternative)	↑	→	→	↑↑

↑↑↑: Markedly elevated; ↑↑: Moderately elevated; ↑: Mildly elevated; →: Normal range.

Comprehensive Interpretation

Analysis of pathway-specific markers revealed distinct activation patterns across disease groups. Classical pathway activation, indicated by elevated C4d fragments and reduced C4 levels, predominated in systemic lupus erythematosus and correlated significantly with disease activity scores ($r=0.724$, $p<0.001$). Alternative pathway markers showed

relatively greater elevation in systemic sclerosis patients, with Bb fragment concentrations 2.3-fold higher than controls compared to 1.6-fold elevation in lupus. Lectin pathway involvement appeared most prominent in Sjögren syndrome, with MBL-MASP complex activity significantly elevated compared to other autoimmune groups.

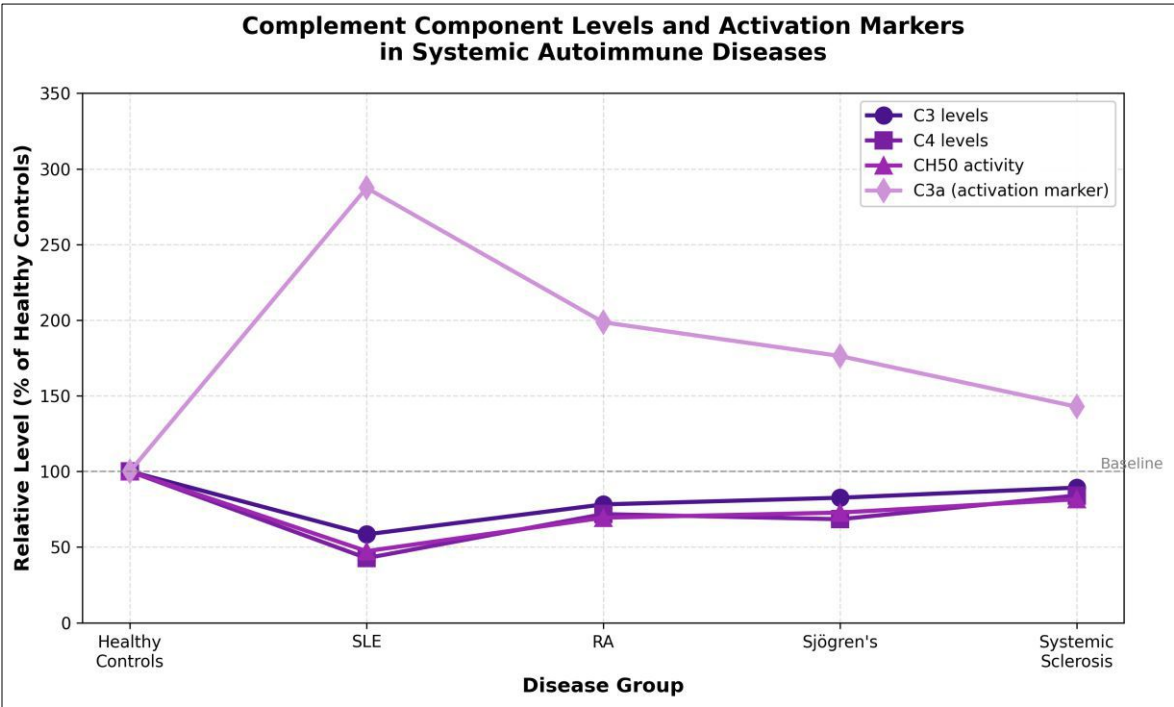


Fig 1: Comparison of complement component levels and activation markers across autoimmune disease groups relative to healthy controls, demonstrating greatest complement consumption in systemic lupus erythematosus.

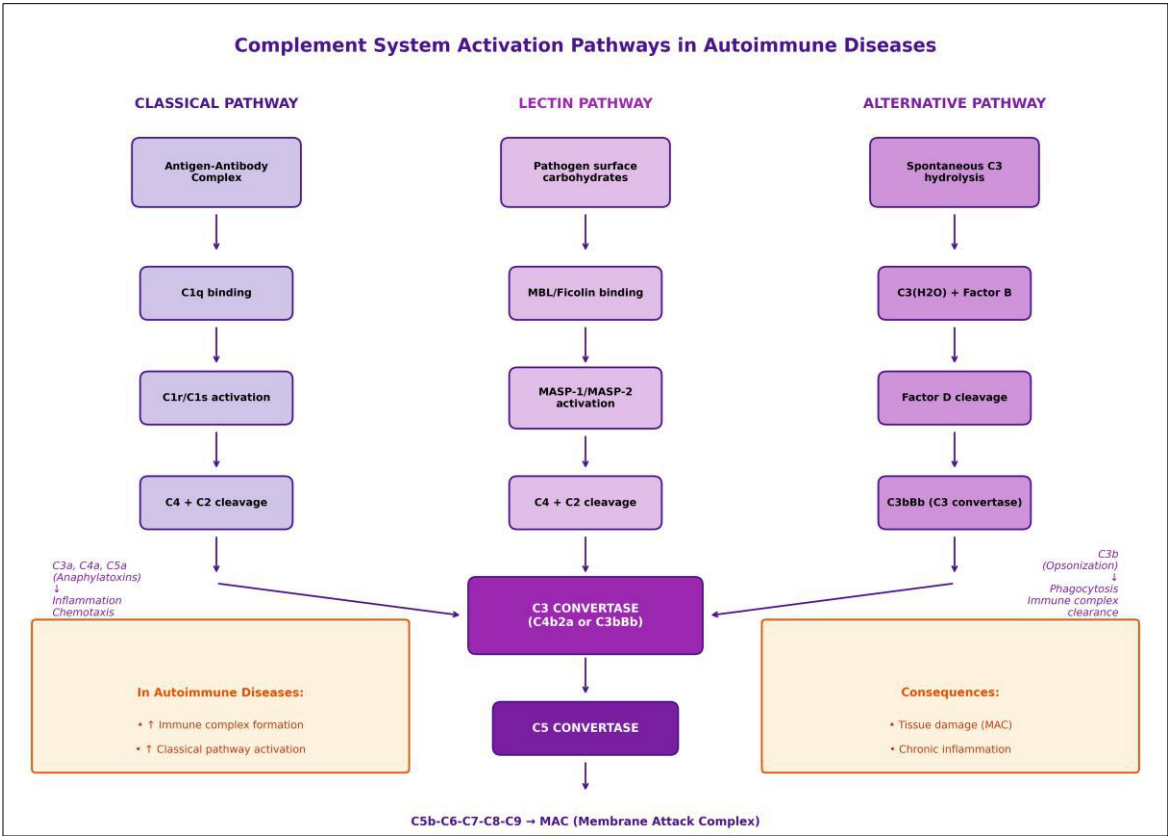


Fig 2: Schematic illustration of complement activation through classical, lectin, and alternative pathways, highlighting convergence at C3 convertase formation and downstream inflammatory consequences relevant to autoimmune pathogenesis.

Discussion

Our findings demonstrate differential patterns of complement pathway activation across major systemic autoimmune diseases, with implications for understanding disease mechanisms and potentially guiding therapeutic interventions ^[18]. The profound complement consumption observed in systemic lupus erythematosus, with C3 and C4 levels reduced to approximately 58% and 43% of normal respectively, confirms the central role of classical pathway activation in lupus pathophysiology. This pattern reflects the abundance of circulating immune complexes characteristic of active lupus that engage C1q and trigger the classical cascade ^[19].

The relatively greater alternative pathway involvement observed in systemic sclerosis represents a novel finding with potential mechanistic implications. Elevated Bb fragments and properdin levels suggest ongoing alternative pathway amplification that may contribute to the microvascular damage characteristic of scleroderma ^[20]. Whether this reflects direct complement attack on endothelial surfaces or secondary amplification of initially classical pathway-mediated activation requires further investigation.

Therapeutic targeting of complement has emerged as a promising strategy for selected autoimmune conditions. Our data suggesting disease-specific pathway predominance supports the rationale for pathway-selective interventions rather than broad complement inhibition ^[21]. Patients with lupus nephritis might benefit most from classical pathway or C3 inhibition, while those with systemic sclerosis could potentially respond to alternative pathway blockade.

The correlation between complement activation markers and disease activity scores, particularly in lupus and rheumatoid arthritis, supports the utility of complement measurements for monitoring disease status and treatment response. Serial complement assessments may help identify patients at risk for disease flares before clinical manifestations become apparent.

Conclusion

This research characterizes differential complement pathway activation patterns across major systemic autoimmune diseases. Classical pathway activation predominates in systemic lupus erythematosus and rheumatoid arthritis, while alternative pathway involvement appears more prominent in systemic sclerosis. These findings enhance understanding of complement-mediated pathogenesis in autoimmunity and support the development of pathway-selective therapeutic strategies. Complement biomarkers correlate with disease activity and may serve as useful monitoring tools in clinical practice. Future research should evaluate whether complement pathway profiling can guide selection of targeted therapies in individual patients with autoimmune diseases.

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