Pathogenicity of Autoantibodies in Rheumatic and Autoimmune Diseases: Lessons from Passive Transfer and Active Immunization Models

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ABSTRACT In this review article, we evaluated experimental evidence supporting the pathogenic role of autoantibodies in rheumatic diseases and selected non-rheumatic autoimmune disorders. We conducted a narrative mechanistic review focusing on experimental studies, which employed passive transfer of patient-derived immunoglobulins or active immunization with defined autoantigens capable of reproducing disease-relevant phenotypes in vivo or ex vivo. Strong experimental evidence supports direct pathogenicity for several rheumatologic autoantibodies, including anti-citrullinated protein antibodies (ACPA), anti-myeloperoxidase (MPO) ANCA, anti-β2-glycoprotein I, anti-Ro/SSA, and anti-ribosomal P antibodies. These autoantibodies induce tissue-specific injury through mechanisms involving complement activation, Fcγ receptor engagement, inflammatory amplification, and antigen accessibility. Representative non-rheumatic autoimmune models, including pemphigus vulgaris, neuromyelitis optica spectrum disorder, and myasthenia gravis, further reinforce the generalizability of antibody-mediated tissue injury across autoimmune medicine. Passive transfer and active immunization studies provide compelling evidence that selected autoantibodies are not merely biomarkers, but active mediators of tissue injury under permissive biological conditions. These findings support the development of targeted therapies directed against pathogenic antibodies, complement pathways, and Fc-mediated effector mechanisms across rheumatic and autoimmune diseases.

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Autoantibodies are central to the diagnosis, classification, and prognostic stratification of autoimmune diseases, particularly in rheumatology. However, whether these antibodies merely reflect immune dysregulation or directly mediate tissue injury has remained a fundamental question in autoimmunity research for decades [1-4]. Experimental systems based on passive transfer of purified immunoglobulins or active immunization with defined autoantigens have progressively clarified this debate, providing direct functional evidence that selected autoantibodies can reproduce disease-relevant phenotypes in vivo.

The conceptual framework supporting autoantibody pathogenicity derives largely from the Witebsky–Rose criteria for autoimmune disease, which emphasize disease reproduction after transfer of autoreactive antibodies or immunization with the relevant antigen [2]. In rheumatology, several autoantibodies fulfill important components of these criteria, including anti-citrullinated protein antibodies (ACPA), anti-myeloperoxidase (MPO) ANCA, anti-β2-glycoprotein I (β2GPI), anti-Ro/SSA, and anti-ribosomal P antibodies. These antibodies can induce inflammation, thrombosis, bone loss, neuronal dysfunction or conduction abnormalities under permissive biological conditions.

Importantly, analogous paradigms have emerged in non-rheumatic autoimmune diseases such as pemphigus, myasthenia gravis, and neuromyelitis optica spectrum disorder (NMOSD). These paradigms support the concept that antibody-mediated pathogenicity represents a conserved mechanism across organ-specific and systemic autoimmunity. In this review, we summarized the main passive-transfer and active-immunization models supporting autoantibody pathogenicity, focusing primarily on rheumatologic diseases while integrating selected non-rheumatic paradigms that reinforce broader mechanistic principles.

METHODS

This narrative mechanistic review is focused on experimental studies evaluating autoantibody pathogenicity through passive transfer of patient-derived immunoglobulins or active immunization with defined autoantigens. Priority was given to studies reproducing disease-relevant phenotypes in vivo or ex vivo, including histopathologic changes, organ dysfunction, or validated clinical manifestations. Seminal mechanistic and translational studies in rheumatology and selected non-rheumatic autoimmune diseases were preferentially included.

EXPERIMENTAL EVIDENCE OF PATHOGENIC AUTOANTIBODIES IN RHEUMATOLOGY

The principal passive-transfer and active-immunization models in rheumatologic diseases are summarized in Table 1.

AUTOANTIBODIES TO CITRULLINATED PROTEINS IN RHEUMATOID ARTHRITIS

Among the autoantibodies associated with rheumatoid arthritis (RA), anti-citrullinated protein antibodies (ACPA) provide some of the strongest evidence for direct pathogenicity. Experimental studies have demonstrated that human ACPA directed against citrullinated vimentin promote osteoclast differentiation and bone resorption both in vitro and in vivo [5]. Injection of purified ACPA into mice induced systemic bone loss even in the absence of overt synovitis, suggesting that autoantibody-mediated skeletal injury may precede clinically apparent arthritis.

Additional studies showed that polyclonal or monoclonal ACPA can induce persistent pain-like behavior independent of overt inflammation [6]. Mechanical hypersensitivity was associated with chemokine-mediated nociceptive activation, supporting the concept that ACPA

Table 1. Passive transfer models demonstrating autoantibody pathogenicity in rheumatic diseases

Autoantibody	Target antigen	Disease / phenotype reproduced	Species / experimental model	Key pathogenic findings	Mechanistic pathways	Ref.
Anti-MPO ANCA	Myeloperoxidase	Necrotizing crescentic glomerulonephritis; systemic vasculitis	Mouse (IgG passive transfer)	Purified anti-MPO IgG induces pauci-immune GN and pulmonary capillaritis	Neutrophil priming, ROS, NETs, endothelial injury	[7,8]
ACPA (anti-vimentin)	Citrullinated vimentin	Bone loss; osteoclastogenesis	Mouse (human IgG transfer)	Direct induction of osteoclast differentiation and bone resorption	Fcγ receptor signaling on osteoclast precursors	[5]
ACPA (polyclonal)	Citrullinated proteins	Chronic pain sensitization	Mouse	Persistent pain independent of synovitis	Chemokine-dependent nociceptor activation	[6]
Anti-β2GPI	β2-glycoprotein I	Arterial thrombosis	Mouse	Accelerated thrombosis and larger thrombi	Complement activation, tissue factor expression, NETs	[9-11]
Anti-β2GPI	β2-glycoprotein I	Pregnancy loss	Pregnant mouse	Fetal resorption and placental injury	Complement-mediated placental damage	[9-11]
Anti-Ro52	Ro52/TRIM21	Congenital heart block	Rabbit fetal heart perfusion	Atrioventricular conduction delay	Calcium-channel interference	[12]
Anti-Ro52	Ro52/TRIM21	Congenital heart block	Human cohort–guided models	Epitope-specific pathogenicity	Apoptosis-associated antigen exposure	[13,24,25]
Anti-ribosomal P	Ribosomal P proteins	Cognitive impairment	Mouse	Memory impairment after blood–brain barrier disruption	Synaptic dysfunction	[14]
Anti-ribosomal P	Ribosomal P proteins	Electrophysiological abnormalities / seizures	Rat (ICV injection)	Epileptiform discharges and neuronal dysfunction	Altered neuronal excitability	[15]
Anti-ribosomal P	Ribosomal P proteins	Depression-like behavior	Mouse	Limbic-system dysfunction	Neuronal binding	[16]

ACPA = anti-citrullinated protein antibodies, ANCA = antineutrophil cytoplasmic antibodies, APS = antiphospholipid syndrome, BBB = blood–brain barrier, β2GPI = beta-2 glycoprotein I, GN = glomerulonephritis, IgG = immunoglobulin G, MPO = myeloperoxidase, NETs = neutrophil extracellular traps, ROS = reactive oxygen species

contribute directly to pain generation in RA. Together, these findings indicate that ACPA are not simply biomarkers of disease but active mediators of bone remodeling and nociceptive dysfunction.

ANTI-MPO ANCA IN SMALL-VESSEL VASCULITIS

Among rheumatic diseases, ANCA-associated vasculitis provides perhaps the strongest direct evidence that circulating autoantibodies can initiate destructive inflammatory disease. Passive-transfer experiments using purified anti-MPO antibodies reproduced pauci-immune necrotizing glomerulonephritis and pulmonary capillaritis closely resembling the human condition [7,8]. Importantly, these models demonstrated dose-dependent disease induction and strong specificity, as control immunoglobulins failed to generate comparable vascular injury.

These experimental systems also clarify the importance of innate immune amplification in autoantibody-mediated pathology. ANCA activates primed neutrophils and monocytes, triggering oxidative burst, degranulation, endothelial adhesion, and neutrophil extracellular trap formation, all of which contribute to vascular injury and propagation of inflammation. The frequent requirement for inflammatory priming in these models supports a second-hit paradigm in which autoantibodies cooperate with infections, cytokine activation, or other environmental triggers to induce overt vasculitis.

SEVERAL AUTOANTIBODIES ARE DIRECTLY PATHOGENIC, NOT ONLY BIOMARKERS. EXPERIMENTAL MODELS SHOW THAT ANTIBODIES SUCH AS ACPA, ANCA, AND ANTI-β2GPI CAN INDUCE TISSUE INJURY AND DISEASE MANIFESTATIONS.

ANTI-β2-GLYCOPROTEIN I ANTIBODIES IN ANTIPHOSPHOLIPID SYNDROME

Experimental models have established anti-β2GPI antibodies as central pathogenic mediators in antiphospholipid syndrome (APS). Passive transfer of purified anti-β2GPI immunoglobulin G (IgG) into mice accelerates arterial thrombosis and enhances thrombus formation after vascular injury [9]. Similar studies demonstrated fetal resorption and placental injury in pregnant mice exposed to these antibodies.

These effects are amplified by complement activation, tissue-factor expression and neutrophil extracellular traps, indicating that anti-β2GPI antibodies function within a broader prothrombotic inflammatory network [10,11]. Such models provide mechanistic support for current therapeutic strategies targeting complement and antibody-mediated pathways in APS.

ANTI-RO/SSA ANTIBODIES AND CONGENITAL HEART BLOCK

Autoimmune congenital heart block (CHB) represents a prototypical form of passively acquired autoimmunity. Maternal anti-Ro/SSA antibodies cross the placenta and may injure the fetal conduction system during a restricted developmental window. Experimental studies using isolated perfused rabbit hearts demonstrated that IgG from mothers of affected children induces atrioventricular conduction abnormalities, particularly when directed against Ro52 epitopes [12].

Epitope-mapping studies further showed that specific Ro52 and Ro60 antibody profiles are preferentially associated with fetal cardiac injury [13]. These observations support a model in which antibody specificity, tissue accessibility, and developmental susceptibility converge to determine pathogenicity.

ANTI-RIBOSOMAL P ANTIBODIES IN NEUROPSYCHIATRIC LUPUS

Anti-ribosomal P antibodies have been strongly associated with neuropsychiatric manifestations of systemic lupus erythematosus (SLE). Experimental studies demonstrated that purified anti-P antibodies impair memory and alter neuronal excitability once access to the central nervous system is permitted [14,15]. Intracerebroventricular administration of anti-P antibodies in rodents induces electrophysiological abnormalities, seizures, and behavioral changes, while injection of an unrelated control IgG does not reproduce the neurological abnormalities induced by anti-P antibodies.

Additional models demonstrated depression-like phenotypes associated with antibody binding to limbic structures [16]. Together, these studies support a direct pathogenic role for anti-ribosomal P antibodies in selected neuropsychiatric manifestations of SLE.

ANTISYNTHETASE AND ANTI-COLLAGEN V ANTIBODIES

Experimental immunization with histidyl-tRNA synthetase induces inflammatory muscle and lung disease resembling antisynthetase syndrome, supporting a role for humoral immunity in myositis-associated interstitial lung disease [17]. Likewise, immunization with collagen V produces fibrosis, vasculopathy and immune activation resembling systemic sclerosis, suggesting that extracellular matrix autoimmunity may contribute directly to fibrotic remodeling [18].

REPRESENTATIVE NON-RHEUMATIC AUTOIMMUNE MODELS

Representative non-rheumatic autoimmune diseases with experimentally demonstrated antibody-mediated pathogenicity are summarized in Table 2. Table 3 highlights the reproducibility of antibody-mediated tissue injury across different medical specialties.

PEMPHIGUS VULGARIS

Pemphigus vulgaris remains historically one of the most convincing demonstrations that autoantibodies alone can reproduce human autoimmune disease. Passive-transfer experiments established that desmoglein-specific IgG directly induces acantholysis and epidermal blistering without requiring concomitant cellular immune transfer [19]. Beyond confirming pathogenicity, these models also clarified fundamental mechanisms of tissue injury, including disruption of desmosomal adhesion, keratinocyte signaling abnormalities, and complement-independent antibody-mediated dysfunction.

AUTOANTIBODY PATHOGENICITY DEPENDS ON CONTEXT. EPITOPE SPECIFICITY, COMPLEMENT ACTIVATION, FC-MEDIATED EFFECTS, AND INFLAMMATORY SECOND HITS INFLUENCE DISEASE EXPRESSION.

Importantly, pemphigus models helped establish conceptual standards subsequently applied across autoimmune medicine. The ability of patient-derived IgG to reproduce highly specific histopathologic features provided one of the clearest validations of the Witebsky–Rose framework in human disease. These studies therefore remain foundational not only for dermatology, but for the broader field of autoantibody pathogenicity.

NEUROMYELITIS OPTICA SPECTRUM DISORDER

In neuromyelitis optica spectrum disorder (NMOSD), passive transfer of aquaporin-4 IgG into rodents with transient blood–brain barrier disruption reproduces astrocytic injury, complement deposition, and demyelinating lesions characteristic of human disease [20]. These models demonstrate that AQP4-IgG directly mediates complement-dependent astrocytopathy.

Table 2. Active immunization models demonstrating autoantibody-mediated disease in rheumatology

Immunizing antigen	Autoantibodies generated	Disease phenotype	Species	Key findings	Mechanisms	Ref.
Histidyl-tRNA synthetase	Anti-Jo-1	Myositis and ILD	Mouse	Muscle and lung inflammation	Autoantigen-specific T–B cooperation	[17,26,27]
Type V collagen	Anti-collagen V	Systemic sclerosis-like fibrosis	Mouse	Skin/lung fibrosis and vasculopathy	Extracellular matrix autoimmunity	[18]
β2-glycoprotein I	Anti-β2GPI	APS-like thrombosis	Mouse	Thrombosis following inflammatory second hit	Complement activation and NET formation	[9-11]
Citrullinated peptides	ACPA	Bone loss and pain sensitization	Mouse	Osteoclast activation and nociceptive sensitization	Fc-dependent signaling	[5,6]

ACPA = anti-citrullinated protein antibodies, APS = antiphospholipid syndrome, β2GPI = beta-2 glycoprotein I, ILD = interstitial lung disease, NET = neutrophil extracellular trap

Table 3. Experimental models demonstrating pathogenicity of autoantibodies in non-rheumatic autoimmune diseases

Specialty	Disease	Autoantibody	Experimental Model	Species	Key findings	Ref.
Dermatology	Pemphigus vulgaris	Anti-desmoglein IgG	Passive IgG transfer	Neonatal mouse	Suprabasal acantholysis and blister formation reproducing human disease	[19]
Neurology	Neuromyelitis optica spectrum disorder	Anti-AQP4 IgG	Passive transfer with complement	Rat	Astrocytic injury = complement deposition and demyelination	[20]
Neurology	Myasthenia gravis	Anti-AChR antibodies	Passive IgG transfer	Mouse	Neuromuscular transmission defects and muscle weakness	[21]

AChR = acetylcholine receptor, AQP4 = aquaporin-4, IgG = immunoglobulin G, NMOSD = neuromyelitis optica spectrum disorder

MYASTHENIA GRAVIS

Myasthenia gravis represents a paradigmatic antibody-mediated neurological disease. Passive transfer of anti-acetylcholine receptor antibodies induces muscle weakness and neuromuscular transmission defects in experimental animals [21]. Complement activation and receptor internalization contribute substantially to tissue injury, explaining the efficacy of antibody-targeted therapies in clinical practice.

ADDITIONAL TRANSLATIONAL PERSPECTIVES IN RHEUMATOLOGY

An important concept emerging from experimental autoantibody research is that pathogenicity may precede clinically overt disease by several years. In rheumatoid arthritis, ACPA positivity is detectable long before synovitis becomes clinically apparent and correlates with subclinical bone loss and altered pain processing [5,6]. These observations support the idea that autoantibodies participate not only in perpetuating inflammation but also in shaping early tissue vulnerability and disease trajectory. Similarly, in antiphospholipid syndrome, anti-β2GPI antibodies may remain clinically silent until additional prothrombotic or inflammatory triggers precipitate overt vascular events [9-11].

THESE MODELS SUPPORT TARGETED THERAPIES. EXPERIMENTAL FINDINGS PROVIDE RATIONALE FOR TREATMENTS DIRECTED AGAINST B CELLS, COMPLEMENT PATHWAYS, AND FC-MEDIATED MECHANISMS.

Another major implication concerns disease heterogeneity. Experimental studies consistently demonstrate that not all autoantibody-positive individuals develop disease, emphasizing that antibody pathogenicity depends on quantitative and qualitative factors including epitope specificity, affinity maturation, Fc glycosylation patterns, complement-fixing capacity, and accessibility to target tissues. This finding is particularly evident in anti-Ro/SSA-associated congenital heart block, where only selected maternal antibody profiles are associated with fetal conduction abnormalities [12,13]. Such findings reinforce the need for more refined serological characterization beyond simple antibody positivity.

Experimental models also clarify why therapies targeting humoral immunity have transformed management of several autoimmune diseases. B-cell depletion therapy in ANCA-associated vasculitis, FcRn inhibition in myasthenia gravis, and complement blockade in NMOSD directly align with mechanisms identified in passive-transfer studies [7,8,20,21]. Similarly, intravenous immunoglobulin exerts broad immunomodulatory effects through Fc receptor saturation, complement modulation and neutralization of pathogenic antibodies, mechanisms repeatedly implicated in experimental autoimmune models.

An additional strength of passive-transfer systems is their capacity to distinguish pathogenic from non-pathogenic autoantibody subsets. In diseases characterized by broad autoantibody repertoires such as SLE, these approaches help explain why some specificities behave predominantly as biomarkers while others directly mediate organ injury. Anti-ribosomal P antibodies, for example, demonstrate clear neurobiological effects under conditions of blood–brain barrier disruption, whereas many other lupus-associated autoantibodies show weaker evidence of direct tissue pathogenicity [14-16].

Future experimental strategies will likely rely increasingly on humanized models and patient-derived monoclonal antibodies. Such approaches may allow precise characterization of pathogenic clones, Fc-dependent functions and interactions between humoral, and innate immunity within tissue-specific microenvironments. Integration of multi-omics technologies with longitudinal clinical cohorts may further identify predictive pathogenic signatures capable of refining individualized therapeutic strategies.

SHARED MECHANISMS AND THERAPEUTIC IMPLICATIONS

Despite disease-specific differences, several shared principles emerge across experimental models of autoantibody pathogenicity. First, antigen accessibility is essential. Autoantigens may become exposed during apoptosis, inflammation, tissue remodeling, or blood–brain barrier disruption. Second, Fcγ receptor engagement and complement activation amplify tissue injury in many antibody-mediated diseases. Third, innate immune activation frequently acts as a critical second hit, thus converting asymptomatic seropositivity into overt disease.

Fine epitope specificity also strongly influences pathogenicity. In congenital heart block, only selected Ro52 profiles confer major fetal risk, while in RA glycosylation and Fc, characteristics modulate ACPA pathogenicity. These observations support the concept that pathogenicity is probabilistic rather than deterministic.

The translational implications are substantial. Experimental evidence supporting direct autoantibody pathogenicity provides a strong rationale for therapies targeting B cells, plasma cells, complement pathways, and Fc-mediated effector functions. Table 4 summarizes the overall strength of evidence supporting the pathogenic role of major autoantibodies according to experimental models and Witebsky–Rose criteria. Clinical success of rituximab,

Table 4. Strength of evidence for autoantibody pathogenicity according to Witebsky–Rose criteria

Autoantibody	Direct pathogenicity	Evidence strength	Disease	Dominant mechanism	Ref.
Anti-MPO ANCA	Yes	Very strong	AAV	Neutrophil-mediated vasculitis	[11-14]
Anti-β2GPI	Yes	Very strong	APS	Thrombosis = complement	[15-22]
Anti-Ro52	Yes	Strong	CHB	Conduction injury	[23-26]
Anti-ribosomal P	Yes (context-dependent)	Moderate–strong	NPSLE	Synaptic dysfunction	[27-30]
ACPA	Yes	Moderate–strong	RA	Bone loss = pain	[6-9]
Anti-dsDNA	Indirect	Moderate	SLE	IC deposition	[30]

AAV = ANCA-associated vasculitis, ACPA = anti-citrullinated protein antibodies, ANCA = antineutrophil cytoplasmic antibodies, APS = antiphospholipid syndrome, CHB = congenital heart block, dsDNA = double-stranded DNA, MPO = myeloperoxidase, NPSLE = neuropsychiatric systemic lupus erythematosus, RA = rheumatoid arthritis, SLE = systemic lupus erythematosus

complement inhibitors, intravenous immunoglobulin, and FcRn blockade aligns closely with mechanisms identified in passive-transfer and active-immunization models.

Future integration of humanized animal models, organoid systems, and patient-derived monoclonal antibodies will likely refine identification of truly pathogenic clones and accelerate development of antigen-specific tolerogenic therapies.

Table 4 summarizes the major pathogenic mechanisms and the strength of experimental evidence supporting autoantibody-mediated tissue injury across diseases.

CONCLUSIONS

Passive transfer and active immunization studies have largely resolved the long-standing debate regarding autoantibody pathogenicity by functionally fulfilling the Witebsky–Rose criteria for autoimmunity. Experimental and translational evidence across rheumatology and other autoimmune fields demonstrates that autoantibodies such as ACPA, anti-MPO ANCA, anti-β2-glycoprotein I, and anti-Ro/SSA are not merely serological markers, but active mediators of tissue injury under permissive immunological and microenvironmental conditions. Similar findings in neurological, dermatological, and hematological autoimmune diseases further reinforce the generalizability of these mechanisms.

These observations refine, rather than replace, the concept of immune tolerance failure. Loss of tolerance generates autoreactivity, whereas specific autoantibodies mediate downstream pathogenic effects. Future integration of humanized models, organoids, and patient-derived monoclonal antibodies with longitudinal clinical studies will be essential to identify truly pathogenic clones and accelerate the development of targeted therapies, including FcRn inhibition, complement blockade, and antigen-specific tolerogenic strategies.

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Capsule

Genomic epidemiology of the 2025 mpox epidemic in Sierra Leone

Campbell and co-authors investigated the genomic epidemiology of the 2025 Mpox epidemic in Sierra Leone. Through viral genome sequencing and epidemiological analysis, the study characterized transmission dynamics, viral evolution, and patterns of geographic spread during the outbreak. The researchers identified multiple transmission chains and evidence of ongoing viral adaptation, while also documenting links between community transmission and regional population movement. The findings underscore the importance of genomic surveillance for outbreak containment and for understanding the evolution of emerging viral pathogens.

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Capsule

Long-term risk of death after tuberculosis diagnosis and treatment

Cerqueira-Silva and colleagues evaluated the long-term mortality risk among individuals diagnosed and treated for tuberculosis. Using large population-based datasets, the investigators found that patients who had completed tuberculosis treatment continued to experience substantially elevated mortality risk for years after therapy compared with the general population. Excess mortality was associated with chronic lung damage, cardiovascular disease, socioeconomic factors, and coexisting medical conditions. The findings suggest that tuberculosis should be viewed not only as an acute infectious disease but also as a chronic condition with lasting health consequences requiring long-term follow-up and integrated care strategies.

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