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REVIEW

Zhou et al: Annexins in autoimmune diseases

Annexins and autoantibodies in autoimmune diseases – Insights into SLE, APS and RA: A review

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ABSTRACT

Autoimmune diseases are becoming increasingly prevalent and can cause multi-organ damage through dysregulated immune responses to self-antigens. This review aims to summarize the roles of annexin family proteins and annexin autoantibodies in the mechanisms of autoimmune diseases, as well as their potential diagnostic and therapeutic applications. A targeted PubMed search conducted on August 31, 2025, utilized annexin- and disease-related terms without year restrictions, focusing on English-language, peer-reviewed studies involving humans or recognized animal models. Evidence suggests that Annexin A1 (ANXA1) and formyl peptide receptor 2 (FPR2) signaling can influence inflammatory and T-cell responses. Additionally, Annexin A2 (ANXA2) is associated with organ-targeted injury, such as lupus nephritis (LN) in systemic lupus erythematosus (SLE), through its interactions with anti-double-stranded DNA antibodies (anti-dsDNA). Annexin A5 (ANXA5) serves as an anticoagulant phospholipid "shield," which can be compromised by antiphospholipid antibodies (aPLs), contributing to thrombosis and obstetric complications in antiphospholipid syndrome (APS) and increasing vascular risk in SLE. In rheumatoid arthritis (RA), ANXA1 exhibits context-dependent effects, while ANXA2 promotes synovial proliferation, invasion, and angiogenesis. Dysregulation of annexins has also been observed in primary Sjögren's syndrome (pSS), multiple sclerosis (MS), and systemic sclerosis (SSc). Additionally, the emerging utility of anti-ANXA1, anti-ANXA2, and anti-ANXA5 autoantibodies for phenotyping and risk stratification, including in seronegative antiphospholipid syndrome (SNAPS), highlights their clinical relevance. Overall, annexins and their autoantibodies represent promising biomarkers and therapeutic targets; however, the heterogeneity of assays and the limited availability of prospective multicenter data currently hinder clinical translation.

Keywords: Annexin family, autoantibodies, autoimmune diseases, systemic lupus erythematosus, antiphospholipid syndrome.

INTRODUCTION

Autoimmune diseases arise from an overactive immune response to self-antigens, leading to tissue and organ damage. These conditions encompass a broad spectrum of disorders, including, but not limited to, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS) and rheumatoid arthritis (RA). Epidemiological studies estimate that approximately 5% of the global population is affected by these diseases, with incidence rates continuing to rise[1–3]. Therefore, in-depth investigation into their pathogenesis, alongside the development of early diagnostic methods and optimized therapeutic strategies, is of paramount importance.

Annexins are a class of calcium-dependent phospholipid-binding proteins involved in crucial biological processes such as vesicular trafficking, autophagy, inflammatory responses, and cell signaling[4,5]. This protein family plays significant roles in various human diseases, including tumorigenesis, female reproductive disorders, obesity, and atherosclerosis[6–10]. Recent studies suggest that specific annexin family members and their autoantibodies are dysregulated in multiple autoimmune diseases, positioning them as potential diagnostic biomarkers and therapeutic targets. However, a systematic summary of the roles of annexins in autoimmune diseases is currently lacking. Consequently, this article aims to review the expression profiles and functional mechanisms of the annexin family in autoimmune diseases to provide a reference for related research.

To support this narrative review, a targeted literature search was conducted in the PubMed electronic database on August 31, 2025. The search strategy was constructed based on the following primary MeSH terms and related keywords: annexin, Annexin A1 (ANXA1), Annexin A2 (ANXA2), Annexin A5 (ANXA5), autoimmune disease, systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), rheumatoid arthritis (RA), primary Sjögren's syndrome (pSS), multiple sclerosis (MS), systemic sclerosis (SSc). The search terms were combined using the Boolean logical operators "AND" and "OR", with no publication year restrictions applied, and the search was limited to English literature. Literature inclusion criteria were as follows: (1) Study subjects: humans or recognized animal models of autoimmune diseases; (2) Study content: involvement of annexin family members or their autoantibodies in expression,

function, or clinical significance; (3) Publication type: published in peer-reviewed academic journals.

THE ANNEXIN FAMILY

The annexin family comprises a group of calcium-dependent phospholipid-binding proteins encoded by multiple genes and conserved in eukaryotes. The human annexin family includes 12 members (A1–A11 and A13)[11,12]. Their canonical structure consists of a conserved C-terminal core domain and a variable N-terminal domain. The core domain typically contains four repeats of approximately 70 amino acids each (annexin A6 contains eight repeats) and harbors characteristic type II Ca^{2+} binding sites, enabling specific recognition and binding to negatively charged phospholipids. The N-terminal domain exhibits significant length polymorphism and sequence diversity, containing various post-translational modification sites that are crucial for regulating annexin function[5,11,13]. This family is implicated in vital functions such as plasma membrane dynamics, inflammation, coagulation, and apoptosis, with A1, A2, and A5 being the most extensively studied members (Table 1).

ANXA1

ANXA1 is a 37 kDa protein composed of 346 amino acids, highly expressed in immune cells (neutrophils, monocytes, macrophages) and various tissues. Its N-terminal domain contains two α-helices arranged at a 60° tilt (Ala^{2}-Asn^{16} and Glu^{18}-Lys^{26}), featuring several functional sites: EGFR/PKC-dependent phosphorylation sites (Tyr21/Ser27), cathepsin D/calpain I cleavage sites (Trp12/Lys26), and a peptide motif (QAWFI) mediating interaction with S100A11[9,14].

ANXA1 exhibits a unique dual role in inflammation. Its anti-inflammatory effects are primarily mediated by glucocorticoids (GCs) and are mediated through binding to formyl peptide receptor 2 (FPR2) of the G-protein coupled receptor family, promoting neutrophil apoptosis, and downregulating the expression of intracellular adhesion molecule (ICAM) and vascular cell adhesion molecule 1 (VCAM1). Under specific conditions (e.g., proteolytic cleavage), ANXA1 can be converted into a pro-inflammatory form. Furthermore, ANXA1 participates in other critical physiological processes, including plasma membrane repair, cell cycle progression, and apoptosis regulation[14–17].

ANXA2

ANXA2 is a 38 kDa protein comprising 339 amino acids. Its N-terminal domain consists of 30 amino acid residues, an acetylation site (Ser1), three phosphorylation sites (Ser11, Ser25, and Tyr23), and an S100A10 binding site. ANXA2 exists as a monomer or a heterotetramer (A2t) in various cell types, including monocytes, endothelial cells, and myeloid cells. The monomer is primarily localized in the cytoplasm, with a minor nuclear fraction, whereas the heterotetramer, formed by two ANXA2 monomers bridged non-covalently by an S100A10 dimer, is typically located beneath the plasma membrane or within the cytoskeletal region[18,19]. This structural diversity and subcellular compartmentalization underlie its multifunctional regulatory capacity.

ANXA2 exerts important biological functions both intracellularly and extracellularly. Intracellularly, it regulates endo-/exocytosis, mediates multivesicular body formation, modulates cell cycle and proliferation, and plays key roles in apoptosis and inflammatory responses. Notably, ANXA2 stabilizes lipid raft structures via interaction with CD44, thereby regulating cell signal transduction through the lipid raft-cytoskeleton axis. Extracellularly, ANXA2 participates in phagocytosis, promotes fibrinolysis, exerts anticoagulant functions, and plays a significant role in angiogenesis[18,20,21].

ANXA5

ANXA5 is a single-chain protein with a molecular weight of approximately 35 kDa, consisting of 320 amino acids. It is the most abundant annexin isoform in nearly all cell types except neurons, primarily expressed by trophoblasts and vascular endothelial cells, and is also widely distributed in other cells, tissues, and the circulation[13,22]. Unlike ANXA1 and A2, its N-terminal domain comprises only about 20 amino acids and lacks canonical post-translational modification sites. This streamlined structure minimizes steric hindrance, allowing the core domain to bind phosphatidylserine (PS) with high affinity, a property fundamental to ANXA5's roles in anticoagulation, cytoprotection, and inflammation regulation[23–25].

THE ANNEXIN FAMILY AND SLE

SLE is a classic chronic systemic autoimmune disease characterized by inflammation and immune-mediated damage to multiple organ systems. Commonly affected organs include the skin and mucous membranes, kidneys, heart, lungs, and the hematopoietic system[26]. Globally, approximately 400,000 individuals are newly diagnosed with SLE annually, predominantly affecting women of childbearing age, with a female-to-male ratio of 9:1[27]. The pathogenesis of SLE is believed to involve interactions between genetic, environmental factors, and immune dysregulation. These complex interactions lead to the production of pathogenic autoantibodies, which form immune complexes (ICs) upon binding their antigens. In SLE, the accumulation of autoantibodies and ICs in various tissues and organs triggers inflammation, ultimately causing damage[28,29]. Recent research suggests that ANXA1, ANXA2, and ANXA5 may play significant roles in SLE pathogenesis and its complications.

ANXA1 and SLE

ANXA1 is known to modulate T-cell receptor (TCR) signaling via binding to FPR2, thereby influencing the T-cell activation threshold[30]. Studies have found that the ANXA1-FPR2 pathway contributes to T-cell activation and differentiation and is involved in SLE development[31]. Animal studies demonstrate that blocking the ANXA1-FPR2 pathway with an ANXA1-specific monoclonal antibody in SLE-prone mouse models suppresses disease symptoms and autoantibody production, prolonging survival[32]. A case-control study in a Southern Tunisian population also indicated associations between ANXA1, FPR1, and FPR2 gene polymorphisms and SLE susceptibility[33]. These findings collectively suggest a role for ANXA1 in SLE pathogenesis.

ANXA2 and SLE

Lupus nephritis (LN) is one of the most severe and common complications of SLE, representing a major risk factor for morbidity and mortality, potentially leading to end-stage renal disease (ESRD)[34]. Over 10% of renal biopsies are diagnosed as LN, affecting approximately 40% of SLE patients[35]. LN is characterized by the accumulation of autoantibodies (primarily anti-dsDNA) in glomeruli and the interstitium, activating the complement system and recruiting immune cells, which

initiates inflammation and eventual organ damage[36]. However, how autoantibodies localize to target organs and induce injury remains incompletely understood. It has been proposed that anti-dsDNA antibodies can bind directly to ANXA2 on mesangial cells, thereby inducing downstream inflammatory processes[37]. Studies show that 65% of anti-dsDNA antibodies isolated from LN patients, and nearly all antibody samples obtained during disease flares, exhibit significant binding to ANXA2. Furthermore, human and murine LN biopsies show co-localization of ANXA2 with ICs in glomeruli, further supporting its pathological association with anti-dsDNA antibodies[38].

ANXA5 and SLE

SLE-associated cardiovascular disease (CVD) can be considered a late-stage complication and a significant contributor to the elevated mortality rate in SLE[39,40]. Independent risk factors for CVD in SLE include traditional factors (age, dyslipidemia, hypertension, diabetes, smoking) and non-traditional factors [antiphospholipid antibodies (aPLs), other SLE manifestations (especially renal), corticosteroid therapy, low levels of natural antibodies][41]. Approximately 30-40% of SLE patients are positive for aPLs[42], aPLs can promote thrombosis by disrupting the anticoagulant shield function of ANXA5[41]. Further research has revealed that since ANXA5 normally binds to vulnerable regions of atherosclerotic plaques to maintain stability, aPL-mediated disruption of ANXA5 increases plaque rupture risk, thereby elevating the risk of myocardial infarction (MI) and stroke in SLE patients[43]. Additionally, oxidized cardiolipin (oxCL), a product of oxidized modification of cardiolipin (CL), exacerbates endothelial dysfunction and thrombosis in SLE patients and synergizes with aPLs to promote CVD[44]. Importantly, ANXA5 can counteract this effect by binding oxCL with high affinity via its phospholipid- binding domain, exerting a protective role[45,46].

THE ANNEXIN FAMILY AND APS

APS is a non-inflammatory autoimmune disorder characterized by the persistent presence of aPLs, with primary clinical manifestations including recurrent arterial and/or venous thrombosis and morbid pregnancy outcomes[47]. APS typically affects relatively young individuals, with a female predominance. The estimated population

prevalence of APS is 0.04–0.05%, with an annual incidence of 0.001–0.002%[48,49]. aPLs are considered the primary effector molecules in APS pathogenesis, mediating characteristic clinical manifestations like thrombosis and obstetric complications through various pathological mechanisms. Notably, the annexin family, particularly ANXA2 and ANXA5, is also recognized to play significant regulatory roles in APS clinical presentations.

ANXA2 and APS

As a common acquired thrombophilia, APS can lead to recurrent arterial and venous thrombosis. ANXA2 is known to function as a receptor on the cell surface, facilitating the assembly of plasminogen and tissue-type plasminogen activator (t-PA), thereby significantly enhancing fibrinolytic capacity[50]. In APS patients, anti-ANXA2 antibodies inhibit this plasminogen-activating function by specifically binding ANXA2, disrupting the dynamic balance of the coagulation-fibrinolysis system and leading to pathological thrombosis[51–53]. Furthermore, ANXA2 on the endothelial cell surface can bind β2-glycoprotein I (β2GPI), forming a stable β2GPI-ANXA2 complex. In susceptible individuals, this complex may stimulate the production of anti-β2GPI antibodies (aβ2GPI). Cross-linking of aβ2GPI with β2GPI within the complex leads to endothelial cell activation, further exacerbating thrombosis[52,54].

ANXA5 and APS

As mentioned earlier (see Section 3.3), aPLs can disrupt the antithrombotic barrier function of ANXA5, thereby increasing the risk of thrombosis[41,55,56]. In APS patients, the interaction between anti-ANXA5 antibodies and ANXA5 also disrupts this anticoagulant barrier, further promoting thrombosis. Additionally, the disruption of the ANXA5 anticoagulant shield on trophoblast cells by aPLs and anti-ANXA5 can induce placental thrombosis, ultimately leading to morbid pregnancy[52,57]. Morbid pregnancy is the second most common clinical manifestation of APS, primarily including recurrent spontaneous abortion (RSA), fetal growth restriction (FGR), preeclampsia (PE), and preterm birth[58]. Notably, the pathogenesis of ANXA5-related morbid pregnancy is not solely attributable to placental thrombosis. In vitro studies show that anti-ANXA5 can promote trophoblast apoptosis and significantly inhibit human chorionic gonadotropin (hCG) secretion by interfering with ANXA5's

physiological functions, and these pathophysiological changes also contribute to morbid pregnancy[8,59]. However, the precise mechanisms of ANXA5 in APS-related obstetric complications are not fully understood and require further investigation.

THE ANNEXIN FAMILY AND RA

RA is a chronic autoimmune disease characterized pathologically by persistent synovial hyperplasia with inflammatory cell infiltration, pannus formation, and cartilage/bone erosion. RA typically presents as symmetric polyarthritis, primarily affecting small joints of the extremities (e.g., metacarpophalangeal, proximal interphalangeal joints), often leading to joint deformity and functional impairment, affecting approximately 0.5–1% of the global population. RA pathogenesis involves multifactorial interactions, including autoimmune dysregulation, inflammatory cascades, genetic susceptibility, and metabolic reprogramming of synovial cells[60-62]. Altered expression of annexin family members in RA patients suggests their potential key roles in disease pathogenesis.

ANXA1 and RA

ANXA1 exhibits a complex dual regulatory role in RA. As a key anti-inflammatory protein induced by GCs, ANXA1 suppresses excessive immune responses in RA by modulating neutrophil and T cell functions and the FPR2 receptor signaling pathway[63]; Concurrently, it inhibits ANXA1–cytosolic phospholipase A2 (cPLA2α) activity, reducing the production of arachidonic acid and its pro-inflammatory metabolites [particularly prostaglandin E2 (PGE2) and leukotriene B4 (LTB4)], while upregulating the anti-inflammatory cytokine IL-10, thereby alleviating synovial inflammation in RA[64,65]. Animal studies further confirm that ANXA1 can improve RA-associated cardiac diastolic dysfunction[66]. However, recent research indicates that ANXA1 may promote RA progression under certain conditions, for instance, activation of the lncRNA-Anrel/miR-146a/ANXA1 axis exacerbates joint inflammation[67]. These findings suggest that the role of ANXA1 in RA is highly context-dependent, warranting further exploration.

ANXA2 and RA

Research shows that the expression and phosphorylation levels of ANXA2 protein are significantly upregulated in the synovial tissue of RA patients compared to healthy

individuals[68]. This aberrant activation may promote disease progression through multiple mechanisms. Recent studies found that the ANXA2/ANXA2 receptor (ANXA2R) axis promotes the secretion of downstream factors such as matrix metalloproteinase-2 (MMP-2), vascular endothelial growth factor (VEGF), and angiopoietin-2 (Ang-2) by activating the Hedgehog (HH) signaling pathway, thereby driving pannus formation[69]. Further research reveals that ANXA2 cooperatively promotes the proliferation and invasion of fibroblast-like synoviocytes (FLS) via the DDR-2/ANXA2/MMP and LncNFYB/ANXA2/ERK1/2 signaling pathways[70-71]. Additionally, ANXA2 can bind the TSP1 domain of connective tissue growth factor (CTGF), forming a CTGF-ANXA2 complex that contributes to FLS proliferation, migration, and angiogenesis, ultimately facilitating pannus formation[72]. In summary, ANXA2 plays a significant role in RA progression.

THE ANNEXIN FAMILY AND OTHER AUTOIMMUNE DISEASES

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease primarily characterized by exocrine gland dysfunction, mainly affecting salivary and lacrimal glands, leading to severe xerostomia and keratoconjunctivitis sicca. Some patients may develop mucosa-associated lymphoid tissue lymphoma (pSS-MALT)[73-74]. Studies show that ANXA2 is overexpressed in the parotid glands of pSS patients, and its expression level gradually increases with disease progression (from pSS to pSS-MALT)[75]. Furthermore, ANXA2 was identified as a key differentially expressed protein in salivary exosomes (EVs) from pSS patients[76]. These findings indicate the potential of ANXA2 as an auxiliary diagnostic and disease activity monitoring biomarker for pSS. Researchers further discovered that, besides ANXA2, ANXA1, A4, A5, and A11 are also upregulated in the salivary and lacrimal glands of SS model mice, suggesting that annexin family members may cooperatively participate in pSS pathogenesis[77].

Multiple sclerosis (MS) is an autoimmune disease of the central nervous system (CNS) characterized by abnormally activated T and B cells mediating myelin damage, triggering inflammation, demyelination, and neurodegeneration, accompanied by blood-brain barrier (BBB) disruption and glial cell activation[78]. Recent studies suggest that ANXA1, via its anti-inflammatory properties, can inhibit glial cell activation and may play a protective role in MS by maintaining BBB integrity and

mitigating neuroinflammation[79-80]. In contrast, ANXA2 exacerbates BBB disruption and promotes the infiltration of peripheral immune cells into the CNS by upregulating cell adhesion molecules ICAM-1/VCAM-1 and regulating cytoskeletal reorganization, ultimately driving disease progression[79,81].

ANNEXIN AUTOANTIBODIES AND AUTOIMMUNE DISEASES

In summary, the annexin family plays significant roles in the pathogenesis of autoimmune diseases (Table 2). Moreover, as a class of emerging serological markers, their corresponding autoantibodies demonstrate multifaceted potential for application in the clinical management of these conditions (Table 3).

Anti-ANXA1 antibodies

Anti-ANXA1 shows significant clinical value in the diagnosis and treatment monitoring of SLE, particularly LN. A study involving 1052 SLE patients found that serum levels of anti-ANXA1 IgG2 were significantly higher in SLE patients with LN compared to healthy controls and correlated directly with anti-dsDNA IgG2 levels, indicating that anti-ANXA1 IgG2 may help identify early or mild LN, possessing discriminative diagnostic value[82]. Furthermore, longitudinal follow-up of newly diagnosed LN patients from disease onset to 36 months revealed that anti-ANXA1 were associated with high proteinuria, and anti-ANXA1 IgG2 levels returned to the normal range within the first 12 months and remained stable over the 36-month follow-up period. This suggests a relatively sensitive response of anti-ANXA1 to treatment, positioning them as a promising candidate biomarker for monitoring LN therapeutic efficacy[83]. However, this conclusion is currently based on a limited number of cohorts and requires further validation.

Anti-ANXA2 antibodies

Anti-ANXA2 holds potential value in APS diagnosis and risk assessment. Current clinical diagnosis of APS requires at least one clinical event history plus the persistent presence of one or more of the following autoantibodies: anticardiolipin (aCL), aβ2GPI, and lupus anticoagulant (LA). These three laboratory tests should be performed concurrently and confirmed positive at least 12 weeks apart[84]. However, some patients present with typical APS clinical manifestations but test negative for these standard aPLs on multiple occasions, a condition defined as seronegative APS

(SNAPS)[85]. To better identify SNAPS, the additive value of "non-criteria" antibodies has gained increasing attention. Known "non-criteria" antibodies include anti-phosphatidylserine/prothrombin, anti-ANXA2/ANXA5, and anti-protein S/protein C antibodies, among others[47,86]. Although sensitivity is relatively low, studies have found that anti-ANXA2 levels are significantly higher in APS patients than in healthy populations, providing important supplementary evidence for SNAPS diagnosis[87-889].

Furthermore, clinical cohort studies demonstrated a positive correlation between serum anti-ANXA2 levels and the incidence of thrombotic events in APS patients[89-90]. Studies in mouse models further support this association[91]. These results suggest that detecting anti-ANXA2 may assist in evaluating thrombotic risk in APS patients.

Anti-ANXA5 antibodies

The clinical value of anti-ANXA5 antibodies has been demonstrated in both systemic sclerosis (SSc) and APS. SSc is a rare autoimmune connective tissue disease characterized by fibrosis of the skin and internal organs and vasculopathy[92]. Studies found that serum anti-ANXA5 levels are significantly higher in SSc patients than in healthy controls, and anti-ANXA5 IgG positivity is associated with more severe digital vasculopathy and lung fibrosis[93–95]. Notably, anti-ANXA5 can remain stably positive for up to 2 years, suggesting its potential for long-term disease monitoring[96].

In APS, anti-ANXA5 are closely related to disease diagnosis and risk assessment. Clinical testing revealed that some SNAPS patients are persistently positive for anti-ANXA5 IgG/M[97-98]. A Chinese cohort study showed increased levels of both anti-ANXA5 IgG and IgM in APS patients, and statistical analysis indicated that detecting anti-ANXA5, particularly anti-ANXA5 IgG, could increase the diagnostic sensitivity for APS[99]. These findings suggest that anti-ANXA5 testing can improve the clinical diagnostic performance for APS, especially providing crucial supplemental value for SNAPS. A clinical study involving 70 patients demonstrated that anti-ANXA5 not only aid in the diagnosis of APS but can also be used to assess patients' thrombotic risk [100]. Moreover, studies utilizing a modified thrombin generation assay found that 40.7% of anti-ANXA5 positive APS patients reached a laboratory thrombogenicity threshold (AUC R $\leq$ 4.5), a proportion significantly higher than in anti-ANXA5

negative patients[101], further indicating the utility of anti-ANXA5 for assessing thrombosis risk. Regarding morbid pregnancy, although multiple studies report a significant association between anti-ANXA5 positivity and the risk of obstetric complications like preterm birth and RSA in APS patients[25，102-105], some studies have not confirmed this link [99,106–108], This highlights the need for deeper research to clarify the specific mechanisms and clinical significance of anti-ANXA5 in obstetric APS.

CONCLUSION AND PERSPECTIVES

Annexins and their autoantibodies play significant roles in various autoimmune diseases (Figure 1). Based on the current evidence synthesized in this review, ANXA1, A2, and A5 demonstrate particularly notable regulatory functions in the pathologies discussed. It is noteworthy that other annexin family members (e.g., ANXA4, ANXA11) may also contribute to regulatory and pathophysiological processes in autoimmunity; however, existing data for these proteins remain insufficient and warrant further investigation. In SLE/LN, ANXA1, ANXA2, and ANXA5 function synergistically, accompanied by a significant increase in anti-ANXA1. APS is characterized primarily by dysregulation of ANXA2 and ANXA5, which is closely associated with the pathogenic roles of anti-ANXA2 and anti-ANXA5. The synovial pathology in RA involves the dual regulatory function of ANXA1 and the ANXA2-mediated processes of synovial hyperplasia and invasion. pSS exhibits upregulation of multiple family members, including ANXA1, A2, A4, A5, and A11, in the salivary glands. In MS, ANXA1 exerts a protective role at the blood-brain barrier, whereas ANXA2 contributes to barrier disruption and promotes disease progression. Although current research has begun to elucidate the mechanisms of the annexin family in autoimmune diseases, the existing evidence system still presents the following main limitations: (1) most clinical data are derived from single-center, small-sample cohorts, and inconsistencies in detection methods and positivity criteria affect the comparability and generalizability of the results; (2) study designs are predominantly cross-sectional, lacking prospective, multicenter, long-term follow-up data to validate their clinical translational value. Based on this, Future studies could focus on the following directions: (1) further clarifying the molecular mechanisms of annexin

family members in various diseases and developing targeted therapeutic strategies against specific annexin pathways; (2) establishing standardized detection systems and conducting multicenter, prospective clinical studies to systematically validate the clinical application value of annexin-related antibodies (e.g., anti-ANXA2, anti-ANXA5) as diagnostic and prognostic biomarkers; (3) conducting in-depth research on the interactions between annexins and other biomolecules as well as inflammatory pathways, to provide a theoretical basis for discovering new disease classification markers and therapeutic targets. The diverse functions of the annexin family in autoimmune diseases make them promising candidates for future precision medicine research. Integrating clinical and basic research holds the potential for their translational application in disease prediction, subtyping, and intervention.

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TABLES AND FIGURES WITH LEGENDS

Table 1. Key features of annexin in autoimmune diseases

Annexin	Amino Acid count	Molecular weight (kDa)	Key functional sites/motifs in the N-terminal domain	Primary functions
ANXA1	346	37	Tyr21/Ser27, Trp12/Lys26, QAWFI.	1. Dual Role in Inflammation. 2. Involvement in plasma membrane repair, cell cycle progression, and apoptosis regulation, among other processes.
ANXA2	339	38	Ser1, Ser11, Ser25, Tyr23, S100A10 binding site.	1. Intracellularly: Regulates endo-/exocytosis, multivesicular body formation, cell cycle and proliferation, apoptosis, inflammatory responses, and cell signal transduction. 2. Extracellularly: Participates in phagocytosis, promotes fibrinolysis, exerts anticoagulant functions, and facilitates angiogenesis.
ANXA5	320	35	Lacks canonical post-translational modification sites.	Involved in anticoagulation, cytoprotection, and inflammation regulation, among other processes.

Abbreviations: ANXA1: Annexin A1; ANXA2: Annexin A2; ANXA5: Annexin A5.

Table 2. Overview of the roles of the annexin family in autoimmune diseases

Annexin	Associated disease(s)	Expression change	Primary function	Related mechanisms
ANXA1	SLE	Upregulated	Involvement in pathogenesis and progression	Modulates T cell activation and differentiation via the ANXA1-FPR2 pathway.
	RA	Not clearly established	Dual role (Anti-inflammatory)	1. Suppresses excessive immune responses via the FPR2 pathway. 2. Inhibits cPLA2α, reducing pro-inflammatory mediators.
			Dual role (Pro-inflammatory)	The lncRNA-Anrel/miR-146a/ANXA1 axis exacerbates inflammation.
	pSS	Upregulated	Involvement in pathogenesis	Acts synergistically with other annexin family members.
	MS	Upregulated	Protective role	Inhibits glial cell activation, maintains BBB integrity, and alleviates neuroinflammation.

ANXA2	SLE	Upregulated in LN	Key target in LN pathogenesis	Binds anti-dsDNA antibodies in glomeruli, forming immune complexes that mediate inflammation and kidney injury.
	APS	Not clearly established	Involvement in pathogenesis and progression	1. Acts as a target for anti-ANXA2, inhibiting fibrinolysis and promoting thrombosis. 2. Forms a complex with β2GPI, stimulating aβ2GPI production, activating endothelial cells, and promoting thrombosis.
	RA	Upregulated	Promotes disease progression	1. Drives pannus formation via HH pathway activation. 2. Promotes FLS proliferation and invasion via DDR-2/ANXA2/MMP and LncNFYB/ANXA2/ERK1/2 pathways. 3. Binds CTGF, synergistically driving disease progression.

	pSS	Upregulated	Potential biomarker	Expression level correlates with disease progression.
	MS	Upregulated	Promotes disease progression	Upregulates ICAM-1/VCAM-1, disrupts the BBB, and promotes immune cell infiltration into the CNS.
ANXA5	SLE	Not clearly established	Protective role	Binds oxCL with high affinity, mitigating endothelial dysfunction and thrombosis.
			Association with complications	aPLs disrupt its anticoagulant shield, increasing CVD risk.
	APS	Not clearly established	Association with complications	1. Disruption of its anticoagulant shield by aPLs or anti-ANXA5 increases thrombosis and/or morbid pregnancy risk. 2. anti-ANXA5 interferes with its function, promoting trophoblast apoptosis and inhibiting hCG secretion, contributing to morbid pregnancy.

	pSS	Upregulated	Involvement in pathogenesis	Acts synergistically with other annexin family members.
ANXA4, ANXA11	pSS	Upregulated	Involvement in pathogenesis	Acts synergistically with other annexin family members.

Abbreviations: aβ2GPI: Anti-β2-glycoprotein I antibodies; aPLs: Antiphospholipid antibodies; ANXA1: Annexin A1; ANXA2: Annexin A2; ANXA4: Annexin A4; ANXA5: Annexin A5; ANXA11: Annexin A11; anti-dsDNA: Anti–double-stranded DNA antibodies; APS: Antiphospholipid syndrome; BBB: Blood–brain barrier; CNS: Central nervous system; cPLA2α: Cytosolic phospholipase A2α; CTGF: Connective tissue growth factor; CVD: Cardiovascular disease; DDR-2: Discoidin domain receptor 2; ERK1/2: Extracellular signal-regulated kinase 1/2; FLS: Fibroblast-like synoviocytes; FPR2: Formyl peptide receptor 2; hCG: Human chorionic gonadotropin; HH: Hedgehog; ICAM-1: Intercellular adhesion molecule 1; LN: Lupus nephritis; lncRNA: Long non-coding RNA; LncNFYB: Long non-coding RNA NFYB; miR-146a: microRNA-146a; MMP: Matrix metalloproteinase; MS: Multiple sclerosis; oxCL: Oxidized cardiolipin; pSS: Primary Sjögren's syndrome; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; VCAM-1: Vascular cell adhesion molecule 1; β2GPI: β2-glycoprotein I.

Table 3. Summary of the roles of annexin autoantibodies in autoimmune diseases

Autoantibody	Associated disease(s)	Expression level	Clinical significance
Anti-ANXA1 (IgG2)	SLE (especially LN)	Elevated, significantly higher in patients with LN	1. Shows potential as a biomarker for identifying early or mild LN. 2. A promising candidate biomarker for monitoring LN therapeutic efficacy; requires further validation.
Anti-ANXA2	APS	Elevated	1. Provides significant supplementary diagnostic value for SNAPS, particularly in conjunction with anti-ANXA5. 2. Association with increased thrombotic risk.
Anti-ANXA5 (IgG/IgM)	APS	Both IgG and IgM elevated	1. Provides significant supplementary diagnostic value for SNAPS, particularly in conjunction with anti-ANXA2. 2. Useful for assessing thrombosis risk. 3. The association with morbid pregnancy remains controversial.
	SSc	Elevated (IgG)	1. Positivity is associated with greater disease severity (digital vasculopathy, lung fibrosis), useful for severity assessment. 2. Potential value for long-term disease monitoring.

Abbreviations: ANXA1: Annexin A1; ANXA2: Annexin A2; ANXA5: Annexin A5; APS: Antiphospholipid syndrome; LN: Lupus nephritis; SLE: Systemic lupus

erythematosus; SNAPS: Seronegative antiphospholipid syndrome; SSc: Systemic sclerosis.

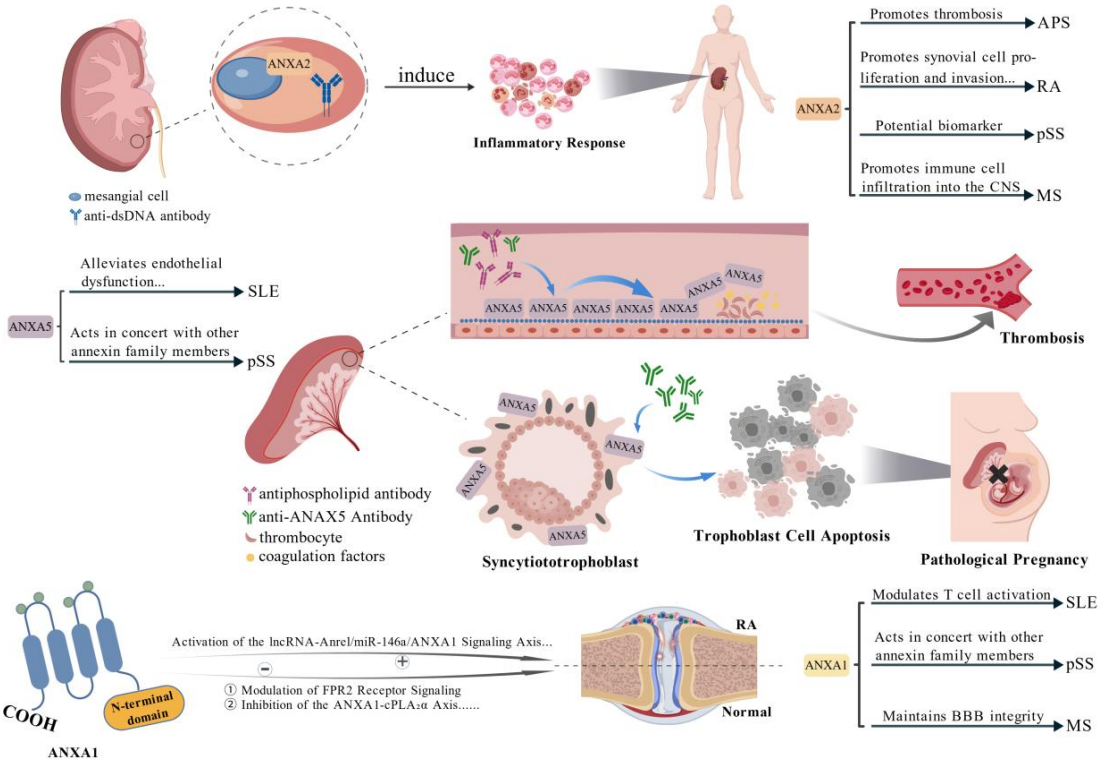

Figure 1. The roles of the annexin family in autoimmune diseases. Schematic summary of disease-associated functions of ANXA2, ANXA5, and ANXA1. ANXA2 is depicted binding nephritogenic anti-dsDNA on mesangial cells to induce an inflammatory response, with indicated links to thrombosis in APS, synovial proliferation/invasion in RA, biomarker potential in pSS, and immune-cell infiltration into the CNS in MS. ANXA5 is shown forming an endothelial/placental anticoagulant "shield" that is disrupted by antiphospholipid antibodies and anti-ANXA5, promoting thrombosis and trophoblast apoptosis leading to pathological pregnancy. ANXA1-related signaling and downstream effects are illustrated alongside its reported roles in SLE, pSS, and maintenance of BBB integrity in MS. *This figure was generated using BioGDP.com*[111]. Abbreviations: ANXA1: Annexin A1; ANXA2: Annexin A2; ANXA5: Annexin A5; anti-dsDNA: Anti–double-stranded DNA antibodies; APS: Antiphospholipid syndrome; BBB: Blood–brain barrier; CNS: Central nervous system; MS: Multiple sclerosis; pSS: Primary Sjögren's syndrome; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus.