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Review

Biophysical regulation of extracellular matrix in systemic lupus erythematosus

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Abstract: Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease characterized by immune dysregulation and multi-organ damage. Recent advances have underscored the critical involvement of extracellular matrix (ECM) biophysical properties in shaping immune cell behavior and metabolic states that contribute to disease progression. This review systematically delineates the pathological remodeling of ECM biophysics in SLE, with a focus on their roles in mechanotransduction, immune-metabolic interplay, and organ-specific tissue injury. By integrating current evidence, we highlight how ECM-derived mechanical cues orchestrate aberrant immune responses and propose new perspectives for targeting ECM-immune crosstalk in the development of organ-specific, mechanism-based therapies for SLE.

Keywords: systemic lupus erythematosus (SLE); extracellular matrix (ECM); mechanotransduction; mechanism; immune regulation; fibrosis; organ-specific damage

Abbreviations: AID: Activation-induced cytidine deaminase; Akt: protein kinase B; ARG1: arginase 1; BLIMP-1: B lymphocyte-induced maturation protein-1; $CD4^+$ T cells: helper T Cells; CXCL13: C-X-C motif chemokine ligand 13; CAT-1: cationic amino acid transporter 1; CD40L: CD40 ligand; COPD: chronic obstructive pulmonary disease; CSR: class switch recombination; CTLs: cytotoxic T lymphocytes; CTSB: cathepsin B; ECM: extracellular matrix; EDPs: elastin-derived peptides; ELR: elastin receptors; FAK: focal adhesion kinase; FRCs: fibroblastic reticular cells; GBM: glomerular basement membrane; HA: hyaluronic acid; HS: heparan sulfate; IFN-α: interferon-alpha; IFP:

interstitial fluid pressure; IκB: inhibitor of kappa B; IKK: IκB kinase; IL-6: interleukin-6; IL-7: interleukin-7; IL-10: interleukin-10; iNOS: inducible nitric oxide synthase; LN: lupus nephritis; LTBP-2: latent transforming growth factor-β binding protein 2; lpr: lymphoproliferation; MMP9: matrix metalloproteinase-9; MRL: Murphy Roths large mouse; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NK: natural killer; NO: nitric oxide; OA: osteoarthritis; pDCs: plasmacytoid dendritic cells; PDGF: platelet-derived growth factor; PF4: platelet factor 4; PI3K: phosphoinositide 3-kinase; RA: rheumatoid arthritis; RGD: arginine-glycine-aspartic acid; SLE: systemic lupus erythematosus; $SPP1^{+}$: secreted phosphoprotein 1; SSc: systemic sclerosis; SWE: shear wave elastography; TAZ: transcriptional co-activator with PDZ-binding motif; TEAD: TEA domain family transcription factors; Tfh: T follicular helper cell; TGF-β: transforming growth factor-beta; TβRII: TGF-β receptor II; TLR2: Toll-like receptor 2; TLR4: Toll-like receptor 4; TNF: tumor necrosis factor; TRAFs: TNF receptor-associated factors; $TREM2^{+}$: triggering receptor expressed on myeloid cells 2; VCAM-1: vascular cell adhesion molecule-1; YAP: Yes-associated protein

1. Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by chronic inflammation and multi-organ involvement, which may ultimately lead to progressive fibrosis in various tissues [1,2]. For a long time, traditional research has mostly focused on the biochemical components of the extracellular matrix (ECM) in SLE [3,4]. However, recent studies have found that the biophysical properties of the ECM, such as stiffness, viscoelasticity, fiber arrangement, and mechanical signal transduction, not only act as a physical scaffold for regulating the positioning of immune cells but also play an active role in the processes of immune dysregulation and tissue damage through mechanisms such as mechanotransduction regulation [5,6]. This review comprehensively and systematically elaborates on the multi-dimensional pathological roles of the ECM in SLE, with a particular focus on the interaction between its biomechanical characteristics and the immunometabolic network. It also delves deeply into the core role of ECM biophysics in the pathogenesis of SLE. To provide a more intuitive understanding of the biophysical regulation of the ECM in SLE, we have designed a simplified schematic illustration (Figure 1).

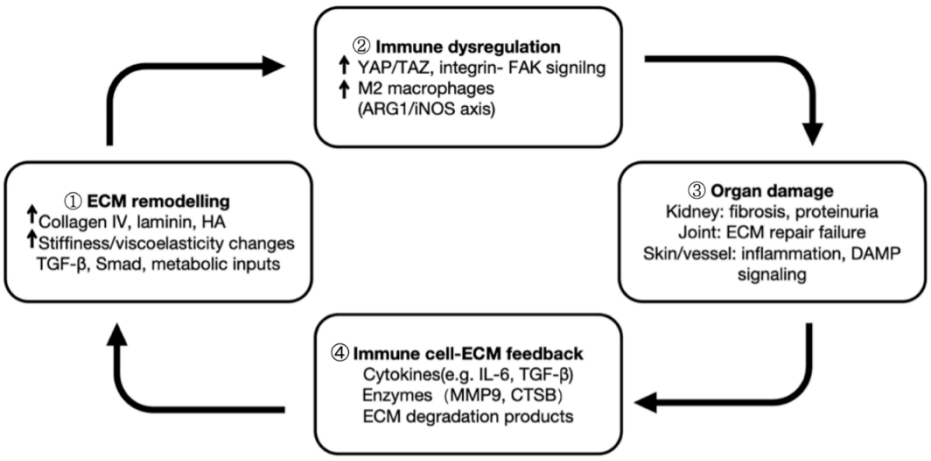

Figure 1. The integrative regulatory axis of ECM remodeling, immune dysregulation, and organ damage in SLE.

2. Discussion

2.1. Pathological alterations of ECM biophysical properties

In SLE, the biophysical properties of the ECM undergo significant pathological alterations that directly contribute to disease onset and progression. Among the various affected organs, the skin and kidneys are not only the most involved target organs in clinical practice but also the most extensively studied in experimental research [7]. Primary ECM changes include excessive collagen cross-linking and component accumulation, leading to a marked increase in tissue stiffness. In this review, the term "high-stiffness microenvironment" refers to a pathological state in which the ECM exhibits increased elasticity, typically characterized by a significantly elevated Young's modulus compared to physiological levels. Under normal conditions, most soft tissues display elastic moduli in the range of 0.1–4 kPa, as observed in organs such as the brain, lungs, and healthy liver and kidneys [8−10]. However, in chronic inflammatory diseases such as SLE, the ECM of affected tissues often undergoes pronounced stiffening. For example, studies have reported that the dermis and subcutaneous muscle layers in the skin of SLE patients exhibit elastic moduli of approximately 35 and 80 kPa, respectively [11]. Similarly, fibrotic liver tissue presents moduli in the range of 20–50 kPa [12], and solid tumors—including lung and pancreatic cancers—can reach 20–40 kPa [13]. In chronic kidney disease, the median modulus of the renal cortex is around 9.4 kPa, significantly higher than the 4.4 kPa observed in healthy controls [14]. These findings suggest that inflammation and fibrotic remodeling broadly alter the mechanical properties of the ECM, leading to the development of abnormally stiff microenvironments. In the MRL/lpr mouse model, which is frequently used in SLE research, the mRNA and protein levels of fibronectin, laminin, and collagen IV in the kidney are significantly upregulated, accompanied by increased ECM stiffness [15]. In humans, shear wave elastography (SWE) studies have shown that the normal cortical stiffness of healthy adult kidneys is 8.23 ± 0.92 kPa, which rises to 12.92 ± 4.50 kPa in fibrotic kidneys [16]. This increase in stiffness is particularly pronounced in lupus nephritis (LN), suggesting that changes in ECM physical properties may serve as a critical biophysical basis for the development and progression of LN.

Beyond structural remodeling, fibrotic ECM induces macrophage polarization toward the immunosuppressive M2 phenotype via signaling pathways such as TGF-β. M2 macrophages secrete anti-inflammatory cytokines like IL-10, promote tissue repair, and suppress excessive immune responses [17]. They also highly express arginase 1 (ARG1), which converts L-arginine into urea and ornithine, depleting extracellular arginine and thereby inhibiting T-cell proliferation [18]. In addition to altering macrophage phenotypes, fibrotic ECM profoundly affects T-cell function by disrupting the arginine metabolic axis [19].

Recent studies have shown that macrophages promote inflammation in stiff microenvironments through activation of YAP, a mechanosensitive transcriptional co-activator [20]. Notably, Cai et al. identified Piezo1, a mechanosensitive ion channel, as a key upstream sensor in macrophages that initiates mechanotransduction in response to ECM stiffness [21]. Piezo1 activation has been linked to increased expression of inducible nitric oxide synthase (iNOS) and suppression of arginase 1 (ARG1), thereby enhancing inflammatory signaling [22]. This Piezo1-driven switch facilitates proinflammatory macrophage polarization in stiff environments, likely through downstream activation of YAP. In contrast, in soft environments, reduced Piezo1 activity permits ARG1 expression, promoting an M2-like, immunosuppressive phenotype [22]. On stiff substrates, Piezo1 activation tends to induce an M1

phenotype, characterized by the upregulation of proinflammatory markers such as iNOS, whereas on softer substrates, it preferentially promotes the expression of anti-inflammatory markers such as ARG1, favoring an M2 phenotype. This reflects a dynamic balance between mechanical and cytokine signaling. These findings suggest that macrophage sensing of fibrotic ECM stiffness and subsequent polarization are, at least in part, mediated by the Piezo1–YAP axis [23].

In fibrotic and inflammatory conditions, elevated iNOS expression leads to the conversion of L-arginine into nitric oxide (NO), which exacerbates arginine depletion and directly impairs T cell survival and effector function [24]. Furthermore, fibrotic ECM may restrict arginine uptake by T cells and antigen-presenting cells through modulation of cationic amino acid transporters such as CAT-1 [25]. Collectively, these metabolic constraints establish an ECM–metabolism–immunity feedback loop: fibrotic ECM promotes M2 polarization and arginine depletion, thereby suppressing T-cell function, while impaired T-cell responses hinder the clearance of autoantigens and perpetuate chronic inflammation, further exacerbating ECM fibrosis. This feedback circuit tightly links ECM mechanical properties with immune dysfunction, offering critical insights into the pathogenesis of SLE.

Fibrotic ECM may also limit the uptake of arginine by T cells and antigen-presenting cells by modulating the expression or activity of cationic amino acid transporters (such as CAT-1) [25]. These metabolic restrictions form an ECM–metabolism–immunity regulatory feedback loop. The fibrotic ECM induces the polarization of macrophages to the M2 phenotype, leading to the consumption of arginine, which is essential for maintaining the function of $CD4^+$ T cells. This, in turn, weakens the immune response of T cells [26], while impaired T-cell activity further weakens the clearance of autoantigens, sustaining chronic inflammation and, in turn, exacerbating ECM fibrosis [27]. This feedback mechanism tightly links the physical properties of the ECM with immune suppression and the progression of SLE, providing a critical perspective for understanding the disease's pathogenesis.

In patients with SLE, abnormal ECM accumulation is closely associated with immune cell metabolic dysregulation, particularly reflected in the aberrant expression of collagen [28], laminin [29], and hyaluronic acid [30]. Elevated levels of collagen peptides in urine are strongly associated with declining renal function [31]. High expression of laminin in glomeruli is frequently accompanied by immune complex deposition [32]. Additionally, excessive accumulation of hyaluronic acid can alter matrix viscoelasticity, disrupt immune cell migration and activation, impair macrophage clearance, and hinder T-cell responses—thereby exacerbating the autoimmune response [33].

As mentioned above, alterations in ECM composition and structure have profound effects on immune cell function. However, beyond these compositional changes, the physical properties of the ECM—such as stiffness and viscoelasticity—can also serve as key signaling cues that actively regulate immune cell behavior and status. In the following section, we will further explore how the mechanical properties of the ECM activate innate immunity through mechanotransduction, thereby driving the inflammatory progression of SLE.

2.2. Mechanical signaling and innate immune activation

Changes in ECM biophysical properties also regulate immune cell functions through mechanical signaling. Recent studies have demonstrated that changes in the stiffness of the ECM, particularly pathological increases in stiffness, can regulate the function of dendritic cells (DCs) through integrin-mediated mechanotransduction pathways [34]. KEGG pathway analysis has revealed that substrate rigidity influences the expression of genes related to metabolism, cytokine signaling, ECM-receptor

interactions, and cell adhesion in DCs [35]. Moreover, stiffer substrates (e.g., 50 kPa) enhance glycolytic metabolism, and the increase in lactic acid production is the result of enhanced glycolytic flux and subsequent pyruvate metabolism [36], which is a hallmark of activated DCs [35]. Mechanical stress has also been shown to upregulate the expression of costimulatory molecules (e.g., CD86, CD40) and MHC class II on the surface of DCs, indicating that their activation status is modulated by the mechanical microenvironment. Integrins, as adhesion receptors, serve as critical mediators in this process by sensing external mechanical cues and transducing them to the cytoskeleton and nuclear signaling axes [37]. More importantly, DCs possess the ability to integrate mechanical stimuli with immune signals, adapting their metabolic programs to support key functions such as migration and antigen presentation [34]. In SLE, dendritic cells—especially plasmacytoid dendritic cells (pDCs)—play a pivotal role in orchestrating autoimmune responses [38]. In SLE patients, immune complexes are internalized by pDCs via endosomal receptors such as TLR7 and TLR9, triggering robust production of type I interferons, particularly IFN-α [39], which further amplifies immune activation. Taken together, these findings suggest that in SLE, abnormally increased ECM stiffness may enhance the metabolic activity and immune responsiveness of pDCs through a "mechanical pre-activation" mechanism. This, in turn, may potentiate their sensitivity to endogenous nucleic acid-containing immune complexes, promote IFN-α production, and exacerbate autoimmune responses.

In SLE, changes in the viscoelastic properties of the ECM within lymphoid organs are considered key factors influencing immune cell function and immune responses [31,40]. Recent studies have shown that the viscoelasticity of ECM, particularly the mechanical properties determined by collagen composition and cross-linking degree, can profoundly regulate the behavior of immune cells. ECM-derived hydrogels with low viscoelasticity (such as FDM-gel) can promote M2 polarization of macrophages, alleviate inflammation, and enhance tissue repair capacity [41]. Low-viscosity ECM can also regulate the differentiation trajectory of T cells through mechanical signals, promoting their transformation into a memory phenotype. This enables them to rapidly expand and exert immune effects upon re-encountering target antigens, thereby providing long-term immune protection [42]. In intestinal models, ECM scaffolds with physiological viscoelasticity and collagen-mimetic properties can regulate the growth status and immune response capacity of intestinal cells and distinguish pathogenic bacteria from probiotics [43]. These findings collectively reveal that the physical properties of the ECM, particularly collagen-related viscoelasticity, are important regulatory factors influencing immune cell function and the tissue immune microenvironment. This section, as summarized in Table 1, reviews the classification and characteristics of major collagen types in the ECM.

Furthermore, there is a bidirectional regulatory relationship between the mechanical properties of the ECM and immune cell functions. Changes in the ECM not only influence immune cell behavior, but the activation of immune cells and the cytokines they secrete can, in turn, affect ECM remodeling and functionality. This bidirectional regulation plays a critical role in tissue damage and immune responses in SLE [44]. These mechanisms form a multidimensional regulatory network of ECM structure–mechanical signaling–immune dysfunction, revealing the complex interplay between tissue microenvironments and immune systems in SLE.

2.3. Mechanical regulation of adaptive immunity

2.3.1. B-cell activation and the CD40L–integrin axis

In SLE, the ECM exerts multilayered regulation over adaptive immune responses through integrin-mediated mechanotransduction. Recent studies have revealed that mechanical alterations of the ECM can directly influence B-cell activation mechanisms, particularly through the synergistic effects of integrins and costimulatory signaling pathways [45,46]. To more intuitively illustrate the molecular mechanism of B-cell activation via the CD40L–integrin axis, Figure 2 visually summarizes the activation pathways and immune effects involved. Studies have shown that B cells are capable of directly sensing ECM stiffness. ECM with high stiffness (22.1 kPa) can significantly enhance the activation level of B cells, while the response induced by ECM with low stiffness (2.6 kPa) is relatively weak. In a high-stiffness environment, the expression of the B-cell surface activation marker CD69 is significantly increased [47]. At the mechanism level, the component of ECM, collagen XIX, binds to integrin αvβ3 and is transmitted intracellularly through the FAK–PI3K–Akt cascade [48]. As a mechanosensitive receptor of the ECM, αvβ3 transmits mechanical signals by recognizing components in the ECM (such as CD90) [49]. On one hand, it directly activates fibroblasts to make them synthesize more ECM [50]; on the other hand, it promotes macrophages to shift toward a profibrotic phenotype and enhances fibroblast activity through factors like TGF-β [51]. The two ultimately synergistically accelerate the pathological remodeling of the ECM [52]. In B-cell immunity, CD40L expressed by activated T cells [especially T follicular helper (Tfh) cells] exerts its effects through a dual-mechanism approach. First, it can directly activate αvβ3, thereby enhancing immune regulation [53]. Second, it triggers B-cell activation by binding to CD40 on the surface of B cells [54]. The integrin–CD40L axis not only promotes humoral immune responses but also drives the production of anti-ECM autoantibodies (such as anti-PF4 antibodies), thereby triggering immune complex–mediated platelet activation and vasculitic responses [55,56]. This axis represents a key mechanistic link in the development of vasculitis in SLE.

Further mechanistic studies have revealed that CD40L is not only expressed on the surface of activated $CD4^+$ T cells but can also be released into circulation in a soluble form, where it forms complexes with integrins (such as αvβ3 and α5β1) [53]. These complexes enhance cell adhesion and co-activate both immune and mechanical signaling pathways. Specifically, binding of CD40L to integrins promotes the recruitment of TRAFs (TNF receptor-associated factors) [57], leading to activation of the IKK complex, which phosphorylates IκBα and releases the NF-κB (p65/p50) heterodimer [58]. This transcription factor then initiates the expression of inflammatory cytokines (e.g., IL-6, TNF-α) and B-cell differentiation regulators (such as BLIMP-1 and AID), significantly enhancing plasma cell formation and autoantibody production [59,60]. Notably, the NF-κB pathway can also upregulate the expression of integrins and CD40L, forming a positive feedback loop that perpetuates autoimmune responses.

Additionally, the CD40L–integrin complex can directly induce platelet activation and upregulate vascular adhesion molecules (such as VCAM-1 and P-selectin), thereby promoting thrombosis in SLE and other autoimmune vasculitides [61,62]. Collectively, the CD40L–integrin axis is a traditional costimulatory pathway that helps T cells assist B cells, but also as a key coupling node that bridges ECM mechanical cues with immune responses—highlighting how the mechanical microenvironment acts as both a modulator and an amplifier of adaptive immunity.

Table 1. Classification and characteristics of major collagen types in ECM.

Collagen type	Structural features	Tissue/location distribution	Functions and characteristics	Disease associations	Relevance to SLE/ECM abnormalities	Ref.
Type I collagen	Fibrillar, thick fiber bundles	Skin, tendons, bones, ligaments, scar tissue, blood vessels, etc.	Provides tensile strength and structural support to maintain tissue stability	Osteogenesis imperfecta, Ehlers–Danlos syndrome	In SLE, abnormal deposition or degradation may affect tissue mechanics and inflammation spread, disrupting T/B-cell migration and activation through altered ECM mechanical signaling in lymphoid organs.	[63]
Type II collagen	Fibrillar, fine fibers	Hyaline cartilage, vitreous body, intervertebral discs	Supports cartilage structure, maintains elasticity and resistance to compression	Osteoarthritis, chondrodysplasia	Less associated with SLE, more relevant to joint pathologies.	[64]
Type III collagen	Fibrillar, reticular microfibers	Vascular walls, skin, visceral organs (e.g., liver, lungs, spleen)	Works with type I to provide elasticity and flexibility; supports expandable tissues and co-distributes with type I collagen	Vascular fragility (e.g., Ehlers–Danlos type IV)	Often shows degradation or imbalance in SLE-associated vasculopathy, potentially altering ECM mechanical cues in lymphoid organs and affecting T/B-cell migration and activation.	[4]
Type IV collagen	Non-fibrillar, network-like structure	Basement membranes (e.g., glomeruli, vascular endothelium, subepithelial layers, skin)	Forms a dense mesh to support basement membrane structure, scaffolds cell migration and signaling	Alport syndrome, renal injury	A classic autoantigen in lupus nephritis; commonly associated with immune complex deposition and basement membrane damage.	[65]

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Collagen type	Structural features	Tissue/location distribution	Functions and characteristics	Disease associations	Relevance to SLE/ECM abnormalities	Ref.
Type V collagen	Fibrillar, co-distributes with type I	Skin, placenta, cornea, bones, and other connective tissues	Regulates the formation and diameter of type I collagen fibers, modulating tissue development	Ehlers–Danlos syndrome, corneal dystrophies	Acts as an autoantigen and triggers inflammation; regulates immune cell infiltration (e.g., affects T-cell penetration by modifying fiber diameter).	[66]
Type VI collagen	Microfibrillar network	Muscle, cartilage, skin, blood vessels	Links cells to ECM, stabilizes matrix structure, supports cell-ECM anchorage and mechanotransduction	Ullrich congenital muscular dystrophy	Expression changes during ECM remodeling affect cell adhesion and migration; involved in immune cell adhesion via integrin signaling.	[67]
Type VII collagen	Anchoring fibrils	Subepidermal junction, skin basement membrane	Works with anchoring fibrils to maintain skin attachment and stabilize basement membrane connection to underlying tissue	Dystrophic epidermolysis bullosa	Contributes to basement membrane disruption and blister formation in cutaneous lupus.	[68]
Type XV collagen	Multi-domain (includes endostatin-like region)	Peribasement membrane (muscle, heart, placenta)	Maintains capillary stability, regulates angiogenesis to preserve tissue homeostasis	Cardiovascular development abnormalities	Susceptible to degradation in inflammatory environments, potentially affecting vascular barrier function.	[69]
Type XVIII collagen	Multi-domain (contains endostatin)	Vascular basement membrane, liver, kidney	Is cleaved into endostatin, which inhibits angiogenesis and regulates tissue development	Knobloch syndrome (ocular malformations)	Degradation products may participate in immune regulation and fibrosis.	[70]

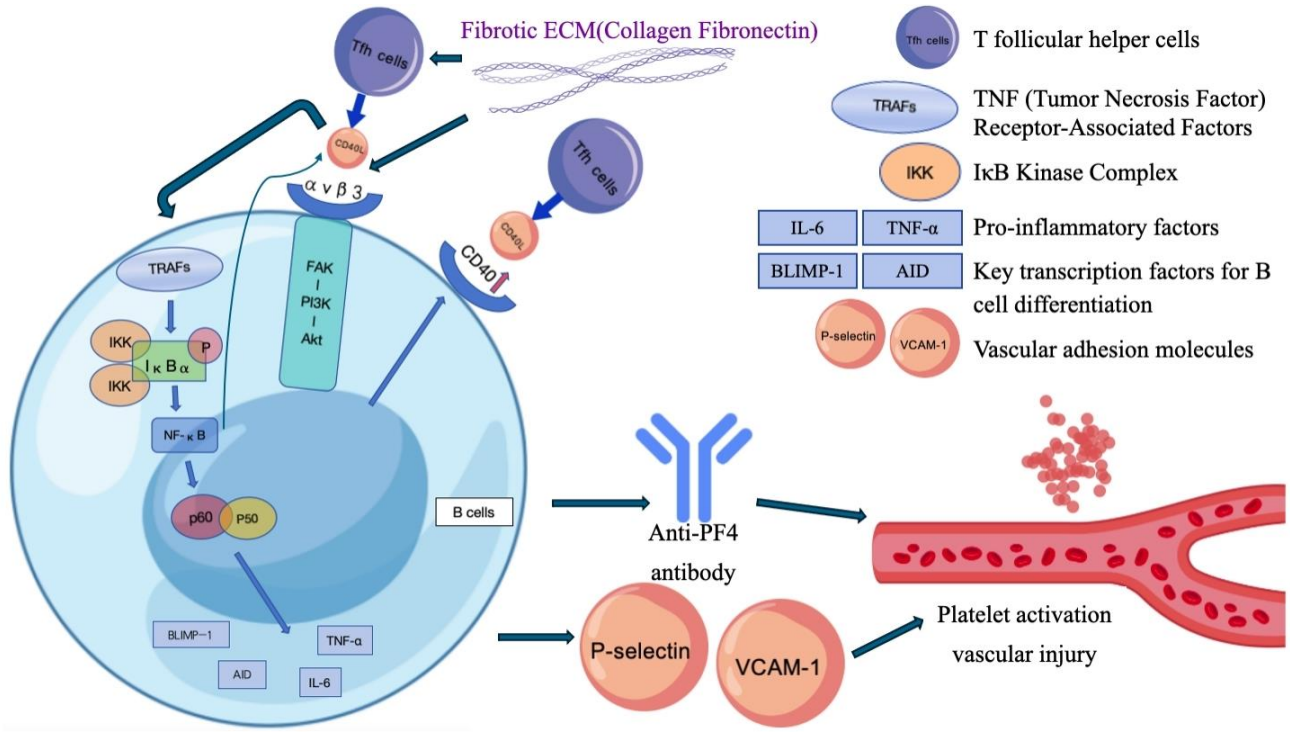

Figure 2. B-cell activation and the CD40L–integrin axis.

2.3.2. T-cell dysfunction and ECM physical barriers

Unlike B cells that are activated via the integrin–CD40L axis, T cells in SLE often exhibit impaired migration and dysfunction due to abnormalities in the physical environment of the ECM. Specifically, the basement membrane, which normally serves as a physical barrier, becomes stiffer in SLE because of excessive collagen deposition and increased cross-linking, significantly restricting T-cell traversal and localization [71]. Previous studies in ovarian and pancreatic cancer models have shown that regions with high collagen density can impede T-cell infiltration from peripheral zones into the core tissue, even when chemokine expression is adequate. Instead, T cells remain confined to the periphery [72,73]. A similar phenomenon likely contributes to the weakened immune surveillance observed in SLE. This localized impairment of directional migration makes it difficult for T cells to promptly encounter and recognize aberrant self-antigens, resulting in self-antigen escape—a process in which abnormal self-components are not effectively cleared, leading to persistent immune activation and driving autoimmune inflammation [74]. In this regard, the structural integrity and function of fibroblastic reticular cells (FRCs) in lymph nodes are also affected by abnormal ECM deposition. FRCs regulate the distribution and activation of T and B cells by forming a reticular scaffold and secreting factors such as IL-7 and CXCL13 [75,76]. However, abnormal ECM deposition can disrupt FRC function, altering their secretion of ECM components, chemokines, and cytokines, ultimately dysregulating immune cell recruitment, activation, and differentiation. This leads to the formation of an immunosuppressive microenvironment [77].

Compared to the traditional view that immune cell functions are primarily regulated by chemical signals, increasing research in recent years has revealed that the physical properties of the ECM also

play a key role in shaping immune cell fate. Especially in autoimmune diseases such as SLE, the ECM not only acts as a physical barrier restricting immune cell migration within tissues but also deeply influences cell activation and effector functions through specific mechanotransduction pathways. This shift in perspective—from a structural restriction to signal regulation—has become an important breakthrough for understanding immune dysfunction and disease progression.

2.3.3. The central role of mechanotransduction pathways

ECM biophysical properties deeply regulate immune cell behavior through mechanical pathways. High-stiffness matrices influence immune cell function through the integrin–FAK/YAP/TAZ signaling axis.

Immune cells sense the stiffness of the ECM through integrins. Upon binding to the ECM, integrin-mediated adhesion promotes the clustering and autophosphorylation of FAK, thereby initiating downstream signaling pathways. In soft matrices, YAP/TAZ are phosphorylated and retained in the cytoplasm in an inactive state, such as ECM substrates with an elastic modulus around 8 kPa, and integrin signaling, actomyosin contractility, and YAP/TAZ activity are suppressed, thereby maintaining YAP/TAZ in an inactive state [78]. However, in stiff matrices, increased matrix rigidity activates YAP/TAZ via the FAK signaling axis, promoting their translocation into the nucleus. Specifically, elevated matrix stiffness can drive YAP/TAZ nuclear translocation and enhance their transcriptional activity by promoting focal adhesion formation and cytoskeletal reorganization [79]. Additionally, in fibrotic environments such as skin fibrosis, stiff ECM can activate YAP/TAZ through the Piezo1–p38 MAPK signaling pathway, thereby further promoting fibrogenesis [80,81]. Once translocated to the nucleus, YAP/TAZ co-activate transcription factors like TEAD to promote genes involved in cell proliferation, immune modulation, and matrix remodeling.

Mechanistically, increased matrix stiffness and YAP/TAZ activation impair immune surveillance by limiting the infiltration and effector function of cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells [82]. Simultaneously, stiff ECM environments promote the polarization of macrophages toward an immunosuppressive M2 phenotype, further suppressing proinflammatory responses [83]. This stiffness-dependent immune modulation represents a critical mechanobiological axis linking ECM remodeling to immune escape and chronic inflammation, particularly relevant in fibrotic and autoimmune conditions such as SLE.

2.4. ECM-driven organ-specific damage

In SLE-associated organ damage, abnormal ECM accumulation and altered mechanical properties are central drivers of pathology.

In LN, immune complex deposition in the glomerular basement membrane and mesangial regions initiates complement activation and triggers local immune-inflammatory responses, leading to the release of profibrotic cytokines such as transforming growth factor-β (TGF-β) and interleukin-6 (IL-6) [84,85]. These cytokines synergistically drive aberrant ECM remodeling within the kidney. Upon binding to its receptor, TβRII (TGF-β receptor II) and TGF-β activate downstream Smad2 and Smad3, which subsequently form a complex with Smad4 and translocate into the nucleus [86]. This complex upregulates the transcription of ECM components such as collagen types I and III and fibronectin, while concurrently suppressing the activity of matrix-degrading enzymes, resulting in excessive ECM synthesis and basement membrane thickening [87].

IL-6 further potentiates TGF-β signaling, sustaining a proinflammatory milieu that promotes mesangial cell proliferation and immune cell recruitment, thereby exacerbating ECM accumulation and structural disorganization [88,89]. Meanwhile, persistent inflammation induces the pathological activation of ECM-degrading enzymes, including matrix metalloproteinase-9 (MMP-9) and cathepsin B (CTSB) [90,91]. Although these enzymes normally maintain ECM homeostasis, their dysregulated expression under chronic inflammatory stress causes non-selective degradation of matrix components. This uncoordinated elevation of both ECM synthesis and degradation disrupts the temporal rhythm of matrix turnover and drives maladaptive fibrotic remodeling.

Clinically, elevated urinary levels of collagen type I- and III-derived peptides reflect this ongoing imbalance in ECM metabolism. These specific degradation products are released during abnormal ECM turnover and are excreted in the urine, serving as non-invasive biomarkers of matrix dysregulation [31]. Studies have shown that urinary collagen peptides are positively correlated with proteinuria severity, glomerulosclerosis, and tubulointerstitial fibrosis in LN patients, suggesting their potential utility as indicators of fibrotic progression [4].

Importantly, ECM alterations are not merely downstream consequences of immune activation but also actively influence immune dynamics. Thickened basement membranes may hinder the efficient clearance of immune complexes, while exposure of abnormal ECM components can act as neo-autoantigens, further perpetuating autoimmunity [32]. This creates a self-reinforcing loop—immune activation leads to ECM remodeling, which in turn amplifies inflammation and fibrosis, further disrupting immune regulation. Ultimately, this cytokine–ECM–immune feedback axis contributes to persistent glomerular injury and proteinuria, hallmark features of LN. A deeper understanding of this interlinked network may offer new therapeutic avenues targeting both inflammation and fibrogenesis in lupus nephritis.

Then, beyond fibrosis driven by metabolism and signaling pathways, could the ECM itself directly participate in immune processes and exacerbate organ damage? As summarized in Table 2, various ECM components in SLE can act as autoantigens, depositing in the glomeruli and triggering inflammatory responses and proteinuria, thereby serving as important sources of autoimmune activation. Studies have shown that type IV collagen and laminin—key structural components of the glomerular basement membrane—are often misidentified as autoantigens, leading to immune complex deposition [92,93]. Fibronectin is upregulated in inflamed tissues, and its antibody levels are closely associated with disease activity [94]. Additionally, HA and its degradation products can activate the TLR4 signaling pathway and contribute to inflammation amplification [30]. Elastin and the proteoglycan, commonly found in skin and vascular lesions, may also be mistaken by the immune system as “non-self”, further aggravating tissue damage [44,95].

This mechanism is similarly observed in SLE-related skin and vascular damage, characterized by abnormal deposition of ECM components (such as collagen and HA), fibroblast activation, and compromised tissue barrier function [96,97]. Ultimately, ECM degradation products can further activate innate immune responses via receptors such as TLR4 and CD44, forming a vicious cycle of matrix breakdown–inflammation amplification (Figure 3) [98].

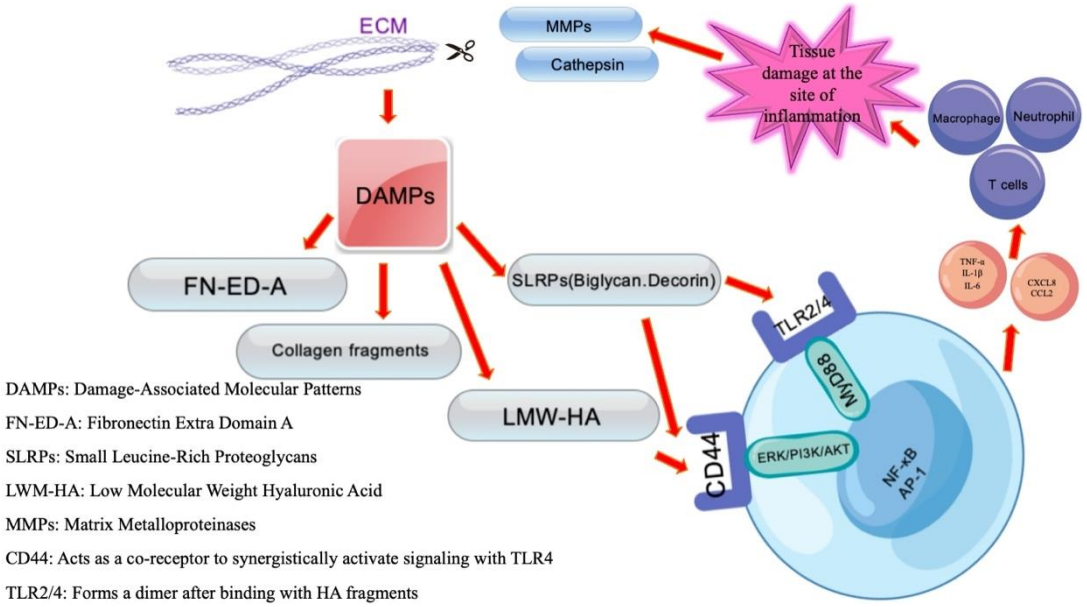

Figure 3. Matrix degradation–inflammation amplification.

ECM-driven organ damage exhibits tissue-specific regulatory features. In rheumatoid arthritis (RA), ECM remodeling is predominantly restricted to the synovial joints and is characterized by pronounced matrix degradation [99]. Fibroblast-like synoviocytes (FLS) and infiltrating immune cells upregulate various matrix metalloproteinases (e.g., MMP-1, MMP-3), leading to cartilage destruction and bone erosion [100]. While immune complex deposition can occur around synovial vasculature, the pathological process is mainly driven by proinflammatory cytokines such as TNF-α and IL-6 and FLS-mediated responses [101,102]. In systemic sclerosis (SSc), the central pathology involves excessive ECM accumulation, particularly of type I and III collagen, affecting the skin, lungs, heart, and kidneys [103,104]. This leads to markedly increased tissue stiffness, impaired perfusion, and progressive organ dysfunction [105]. Fibrotic remodeling is perpetuated by TGF-β–Smad signaling and integrin–FAK-mediated mechanotransduction, establishing a feedforward loop of stiffness-driven fibroblast activation [106,107]. Although immune complex deposition can be observed in small vessel walls, it is not a dominant pathogenic mechanism.

In SLE, ECM remodeling is dynamic and context-dependent, involving both matrix degradation and accumulation across multiple organs. Immune complexes deposit extensively along the glomerular basement membrane, dermal–epidermal junction, and subendothelial regions of small vessels, where they activate complement and trigger inflammation [108]. These complexes often contain ECM components such as type IV collagen and laminin, highlighting the ECM as a reservoir of autoantigens [65,92]. In summary, RA features localized matrix degradation [109], SSc is dominated by progressive ECM accumulation and fibrotic stiffening [110], and SLE integrates both processes and highlights the ECM as a key player in immune activation and metabolic regulation—making it a prototype of complex immune–matrix interplay.

During the occurrence and development of various diseases, there exists a close and dynamic bidirectional regulatory relationship between the ECM and the immune system [111]. Abnormal interactions between the ECM and immune cells often exacerbate pathological conditions [44]. Studies have shown that GM-CSF, IL-17A, and TGF-β1 can induce the differentiation of $SPP1^{+}$ macrophages,

which in turn activate fibroblasts and promote pathological ECM deposition [112,113]. Conversely, stiffened or degraded ECM activates macrophages via integrin-FAK/YAP mechanical pathways to adopt profibrotic phenotypes, forming an "immunity-matrix" positive feedback loop [83]. As previously mentioned, the ECM exhibits tissue-specific pathological remodeling in organs. It is deeply involved in the immune imbalance and organ damage of SLE. However, conventional indices such as SLEDAI and BILAG do not account for the influence of ECM biology on the pathogenesis of SLE. Notably, plasma osteopontin (OPN)—an ECM protein that binds to collagen [114]—has been shown to correlate with SLEDAI scores [115]. In addition, matrix metalloproteinases (MMPs), which degrade ECM components, have also been implicated in SLE disease activity. Specifically, MMP-9 activity is associated with SLEDAI in SLE patients and correlates with BILAG scores in male patients [116]. Incorporating biomarkers such as serum OPN levels and MMP activity alongside traditional indices like SLEDAI and BILAG may enable a more accurate assessment of the dynamic pathological states of SLE.

2.5. ECM-targeted therapeutic strategies

Among various ECM-targeted approaches, collagen-binding nanoparticle systems represent a particularly promising strategy for SLE, due to their ability to exploit the structural specificity of fibrotic lesions. In low-viscoelastic ECM environments, elevated interstitial fluid pressure (IFP) significantly affects immune cell migration and nanoparticle diffusion [117]. Specifically, increased IFP restricts the movement of both cells and nanoparticles within tissues, thereby impairing drug delivery efficiency and immune surveillance [118]. For example, hyaluronic acid (HA), a naturally occurring high-molecular-weight polysaccharide and a key ECM component, forms a highly hydrated matrix due to its strong hydrophilicity [119]. High concentrations of HA markedly reduce the local shear modulus and viscoelasticity of the ECM. Oscillatory shear rheology data show that when HA concentration increases from 0 to 1 mg/mL, the ECM's shear storage modulus (G') drops from 24.3 ± 5.2 to 15.8 ± 3.4 Pa (a reduction of approximately 35%), while the phase angle (δ), which reflects viscoelastic behavior, rises from $4.4 \pm 0.2°$ to $5.7 \pm 0.7°$ (an increase of about 29.5%), indicating a transition toward more fluid-like mechanical behavior [120]. This mechanically weakened microenvironment contributes to elevated IFP, which in turn hinders the intratissue distribution of therapeutic agents and immune cell infiltration. Studies have shown that under elevated IFP conditions, the diffusion coefficient of nanoparticles can decrease by up to 28.9-fold, and the increased viscosity of interstitial fluids further exacerbates the diffusion barrier [121].

In fibrotic autoimmune diseases such as SLE, collagen fibers within the ECM frequently undergo highly ordered directional remodeling, exposing specific spatial conformations and amino acid sequences that serve as natural binding sites for targeted therapies [122]. These structural features not only suggest a potential mechanobiological link between ECM fibrosis and immune activation but also provide a physical foundation for the rational design of precision drug delivery systems [6,123]. Compared to conventional delivery approaches that rely on passive diffusion or nonspecific adsorption, collagen-targeted nanoparticle systems allow precise anchoring of therapeutics at fibrotic stiff tissue, thereby markedly enhancing efficacy and reducing systemic toxicity. This strategy holds great promise as a targeted treatment approach for SLE and related disorders. Such systems have already demonstrated therapeutic potential in various fibrotic conditions. For instance, a chitosan-based nanoparticle exploiting natural collagen affinity effectively delivered siRNA to hepatic stellate cells in liver fibrosis [124], and a liposomal platform integrating ECM-penetrating peptides with pathological

collagen targeting achieved efficient delivery of anti-fibrotic agents to idiopathic pulmonary fibrosis (IPF) lesions [125]. Collectively, these studies support the feasibility and translational potential of collagen-targeted nanocarriers for therapeutic applications in ECM-related diseases.

Another strategy targets the upstream drivers of ECM remodeling, particularly the TGF-β signaling pathway, a central regulator of fibrosis and immune suppression. Small molecule TGF-β receptor kinase inhibitors (e.g., SB-431542) and neutralizing antibodies have demonstrated anti-fibrotic and immunomodulatory effects in lupus-prone mice, although concerns remain regarding systemic side effects and the broad role of TGF-β in immune homeostasis [126].

Additionally, matrix metalloproteinase (MMP) modulators offer a means to directly regulate ECM degradation and remodeling. Selective MMP-9 inhibition, for example, has been shown to attenuate kidney damage and reduce autoantigen exposure in lupus nephritis models [90]. However, due to the complex and context-dependent roles of MMPs in tissue repair and inflammation, therapeutic specificity remains a challenge.

Collectively, ECM-targeted interventions underscore the therapeutic potential of regulating physical properties such as stiffness and fiber alignment and propose the development of more precise biophysics-based treatment strategies for autoimmune diseases. Some studies have shown that traditional animal models have significant differences from humans in terms of ECM composition [127,128], which limits the effectiveness and predictive power of ECM-targeted therapy in transitioning from animal experiments to clinical applications. Therefore, future research should place greater emphasis on evidence based on human clinical data.

Table 2. Examples of ECM proteins as autoantigens in autoimmune diseases.

ECM protein	Structural features	Distribution sites	Functions and characteristics	SLE lesion sites	Other immune-related diseases	Relevance to SLE/autoimmunity	Ref.
Laminin	Basement membrane glycoprotein composed of α/β/γ chain trimers	Basement membrane (e.g., glomeruli, skin)	Contributes to basement membrane formation, maintains tissue barrier integrity	Skin, kidney	Antiphospholipid syndrome	Serves as an autoantigen in SLE; anti-laminin antibodies impair basement membrane integrity, promote complement activation and inflammatory cell infiltration, contributing to tissue injury	[129]
Fibronectin	High-molecular-weight glycoprotein with RGD cell-binding domain	Vascular wall, interstitial tissue	Promotes cell adhesion and migration, involved in tissue repair and ECM remodeling	Skin, vasculitis, kidney	RA	Overexpressed in SLE, associated with immune activation and fibrosis; autoantibodies target fibronectin, forming circulating immune complexes that deposit in glomeruli and vessel walls	[108]
Hyaluronic acid	Non-sulfated glycosaminoglycan forms a hydrated ECM network	Synovial fluid, skin, soft tissues	Regulates cell migration and differentiation, modulates ECM elasticity and hydration	Skin, edematous regions	RA, osteoarthritis	Degradation fragments activate macrophages and dendritic cells via TLR2/4 or CD44, promoting proinflammatory cytokine release and amplifying immune responses in inflamed tissues	[130]

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ECM protein	Structural features	Distribution sites	Functions and characteristics	SLE lesion sites	Other immune-related diseases	Relevance to SLE/autoimmunity	Ref.
Elastin	Highly cross-linked core elastic fiber protein formed from tropoelastin monomers	Skin, blood vessels, lungs	Provides tissue elasticity and extensibility, supports mechanical stability	Skin, vessels	Systemic sclerosis (SSc), large vessel vasculitis, chronic obstructive pulmonary Disease (COPD)	Autoantibodies target elastin cross-linking regions or degradation products; elastin-derived peptides (EDPs) activate macrophages via TLR4 or elastin receptors (ELR), triggering inflammatory responses and contributing to misrecognition in SLE-associated vascular and cutaneous lesions	[131]
Perlecan	Basement membrane proteoglycan with heparan sulfate (HS) side chains and core protein	Basement membrane, vessel walls, cartilage	Stabilizes basement membrane, mediates cell–ECM interactions	Kidney (GBM injury), blood vessels	RA, osteoarthritis	Acts as an autoantigen in SLE skin and vessel lesions; anti-perlecan antibodies target HS chains or core protein and disrupt electrostatic barrier and structural integrity; degradation products activate macrophages via TLR2/4 to promote inflammatory cytokine release	[132]
Fibrinogen	Plasma-derived ECM-associated protein involved in coagulation and inflammation	Plasma, vessel walls, wound sites	Mediates coagulation and wound healing, forms fibrin networks, modulates inflammation	Vasculitis, skin ulcers	RA	Linked to immune complex deposition and tissue damage in SLE; fibrinogen deposits in the ECM are recognized by autoantibodies, activating complement and recruiting neutrophils, exacerbating vascular inflammation and fibrosis	[133]

3. Conclusions and perspectives

In SLE, the pathogenic cascade can be conceptualized as a unifying axis of ECM remodeling–immune dysregulation–organ pathology.

Initially, aberrant activation of the TGF-β/Smad pathway drives fibroblast activation and excessive deposition of collagen IV, laminin, and hyaluronic acid, leading to increased stiffness, reduced porosity, and altered viscoelasticity. These changes reshape the microenvironment and provide the biophysical foundation for immune dysfunction.

Subsequently, in this context, fibrotic ECM influences immunity via mechanotransduction (integrin–FAK–YAP/TAZ signaling) and metabolic rewiring (ARG1/iNOS-mediated arginine depletion). This results in M2 macrophage polarization, B-cell hyperactivation, impaired T-cell migration, and ultimately tolerance breakdown, chronic inflammation, and autoantibody production. It can thus be seen that ECM abnormalities are not only structural lesions but also a direct driving force behind immune imbalance.

The combined effects of ECM abnormalities and immune dysregulation drive organ-specific injury. In LN, ECM accumulation, immune complex deposition, and protease imbalance (MMP9, CTSB) cause GBM thickening and fibrosis. In arthritis, fibroblast-like synoviocytes produce MMP-3, leading to cartilage degradation and synovial fragility. In skin and vasculature, ECM fragments (HA, fibronectin) act as autoantigens or DAMPs, activating TLR4/CD44 and amplifying inflammation.

Collectively, these findings support the notion that the dynamic imbalance of ECM biophysical properties and biochemical composition forms a multidimensional pathological network linking immune dysfunction, metabolic disorders, and organ damage. ECM serves not only as a physical scaffold but also as a central hub regulating immune cell function and metabolic reprogramming. Future research should focus on precisely modulating ECM mechanical properties in SLE. This includes targeting ECM mechanotransduction, developing dynamic ECM monitoring and intervention strategies, organ-specific regulation, and integrating interdisciplinary technologies. A multidimensional understanding of ECM's core role in SLE holds promise for overcoming the limitations of traditional immunosuppressive therapies and may pave the way for restoring immune homeostasis and reversing organ fibrosis.

Use of generative-AI tools declaration

During the preparation of this manuscript, ChatGPT (OpenAI) was used solely for language editing and improving the clarity and readability of the text. The tool was not involved in generating scientific content, analyzing data, or drawing conclusions. All intellectual contributions remain the responsibility of the authors.

Conflict of interest

The authors report no conflicts of interest in the preparation of this manuscript.

Author contributions

Qiwei Li designed the research concept and wrote the manuscript. Qiang Li, Zhaoyang Xiao, and Keiji Naruse contributed to the conception of the study. Ken Takahashi designed and structured the overall research concept.

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