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REVIEW

Endoplasmic Reticulum Stress as a Stage-Dependent Regulatory Hub in Rheumatoid Arthritis

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Abstract: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent synovial inflammation and progressive joint destruction. Beyond its canonical role in maintaining proteostasis, growing evidence indicates that endoplasmic reticulum (ER) stress acts as a dynamic regulatory hub integrating inflammatory signaling, metabolic reprogramming, and cell fate control within the RA synovium. Activation of the unfolded protein response (UPR) sensors—IRE1α, PERK, and ATF6—initially promotes adaptive compensation aimed at restoring ER homeostasis. However, sustained or maladaptive signaling drives inflammatory amplification, apoptosis resistance in fibroblast-like synoviocytes (FLS), immune dysregulation, and enhanced osteoclastogenesis. Recent studies further reveal stage-dependent and cell type–specific patterns of ER stress activation, underscoring its context-dependent pathogenic functions during disease initiation and progression. Accordingly, therapeutic strategies are shifting from broad suppression of ER stress toward precision modulation of discrete UPR modules, including alleviation of excessive proteostatic burden and selective induction of pro-apoptotic signaling in pathogenic synoviocytes. By integrating mechanistic insights with translational perspectives, this review highlights ER stress as a context-dependent signaling network and a potential precision therapeutic target in RA.

Keywords: rheumatoid arthritis, endoplasmic reticulum stress, unfolded protein response, fibroblast-like synoviocytes

Introduction

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by persistent synovial inflammation, progressive cartilage degradation, and irreversible joint damage. Despite substantial advances in biologic agents and targeted synthetic therapies, a considerable proportion of patients exhibit incomplete responses, secondary resistance, or persistent synovial hyperplasia even under adequate immunosuppression.[1,2] These clinical limitations indicate that RA pathogenesis cannot be fully explained by immune dysregulation alone and likely involves additional stress-responsive cellular programs that sustain inflammation and pathological tissue remodeling.[3]

The endoplasmic reticulum (ER) is a central hub for cellular proteostasis and metabolic regulation, coordinating protein folding and maturation, calcium homeostasis, lipid biosynthesis, and the secretory pathway.[4] Disruption of ER homeostasis by inflammatory, metabolic, oxidative, or hypoxic stress conditions leads to an imbalance between protein-folding demand and capacity, resulting in the accumulation of unfolded or misfolded proteins and the induction of ER stress.[5] Cells respond by activating the unfolded protein response (UPR), a conserved signaling network mediated mainly by three ER transmembrane sensors: inositol-requiring enzyme 1 (IRE1α), protein kinase R–like ER kinase (PERK), and activating transcription factor 6 (ATF6).[6] In the short term, UPR activation restores ER homeostasis by enhancing chaperone expression, reducing global protein translation, and promoting ER-associated degradation.[7] However, prolonged or unresolved ER stress can shift the UPR from an adaptive program to a maladaptive response that promotes

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inflammation, metabolic dysfunction, apoptosis resistance, or cell death. This dual nature makes ER stress particularly relevant to chronic inflammatory diseases such as RA.

In the RA synovium, chronic hypoxia, pro-inflammatory cytokines, oxidative stress, metabolic overload, and calcium imbalance disrupt ER proteostasis and sustain UPR activation.[8] Although initially adaptive, sustained ER stress extends beyond protein-folding control and contributes to inflammatory amplification, metabolic remodeling, and cell fate regulation.[9] Importantly, ER stress signaling in RA exhibits pronounced stage-dependent and cell type–specific features.[10] Transient or moderate UPR activation may confer cytoprotective effects,[11] whereas sustained or dysregulated activation, particularly involving the IRE1–XBP1 and PERK–CHOP axes, promotes pathogenic transformation of fibroblast-like synoviocytes (FLS), macrophage cytokine production, T-cell metabolic reprogramming, and osteoclast differentiation.[12,13] This adaptive-to-maladaptive transition positions ER stress as an active regulatory node linking environmental stress, immune signaling, and structural joint damage.[14]

Despite increasing recognition of ER stress involvement in RA, current knowledge remains fragmented. Many studies focus on individual UPR branches or isolated cell populations, lacking an integrated framework that incorporates temporal progression, intercellular crosstalk, and therapeutic translation. Furthermore, the dual and context-dependent roles of ER stress—protective during early adaptation yet pathogenic during chronic activation[7]—raise critical questions regarding whether therapeutic strategies should suppress, fine-tune, or selectively modulate specific UPR components.

In this review, we propose that ER stress functions as a stage-dependent regulatory hub in RA, dynamically transitioning from adaptive compensation to pathogenic remodeling. We integrate canonical UPR signaling with cell type–specific mechanisms, inflammatory circuits, and metabolic reprogramming, and discuss emerging therapeutic strategies centered on precision modulation rather than indiscriminate pathway inhibition. By reframing ER stress within a dynamic and context-dependent model, we aim to provide a conceptual foundation for stage- and cell-specific intervention strategies in RA.

ER Stress Signaling Architecture in Rheumatoid Arthritis

Core UPR Sensors and Signaling Cascades

The UPR is coordinated by three principal ER transmembrane sensors—IRE1α, PERK, and ATF6.[15] Under homeostatic conditions, these sensors remain inactive through association with the ER-resident chaperone GRP78/BiP. Accumulation of misfolded or unfolded proteins within the ER lumen promotes GRP78 dissociation, thereby initiating activation of the three canonical signaling branches (Figure 1).

Upon activation, IRE1α mediates unconventional splicing of X-box binding protein 1 (XBP1) mRNA, generating XBP1s, which induces genes involved in protein folding, ER-associated degradation (ERAD), lipid biosynthesis, and secretory pathway expansion.[16] Sustained IRE1α activation can also trigger regulated IRE1-dependent decay (RIDD) of selected mRNAs and activate stress kinases such as JNK, thereby linking ER stress to inflammatory and apoptotic signaling.[17,18] PERK phosphorylates eukaryotic initiation factor 2α (eIF2α), leading to transient global translational attenuation while selectively enhancing translation of activating transcription factor 4 (ATF4).[19] ATF4 coordinates adaptive programs related to redox homeostasis, amino acid metabolism, and autophagy, whereas prolonged PERK signaling promotes C/EBP homologous protein (CHOP), a key mediator of ER stress–induced apoptosis.[20] Following GRP78 release, ATF6 translocates to the Golgi apparatus and undergoes regulated intramembrane proteolysis to generate an active transcription factor that induces chaperone genes and ERAD components (Figure 1).

Importantly, the three canonical UPR branches—IRE1α, PERK, and ATF6—do not function as independent signaling modules but instead operate as an integrated and interconnected network.[21] For instance, PERK–eIF2α–ATF4 signaling can transcriptionally regulate components shared with other UPR branches, while IRE1α-mediated XBP1 splicing cooperates with ATF6 to induce chaperone expression and ERAD.[22] In addition, IRE1α-dependent RIDD activity and PERK-driven translational attenuation collectively reshape the cellular stress response.[23] Such coordinated interactions enable dynamic tuning of adaptive versus maladaptive outcomes under different stress conditions.[24]

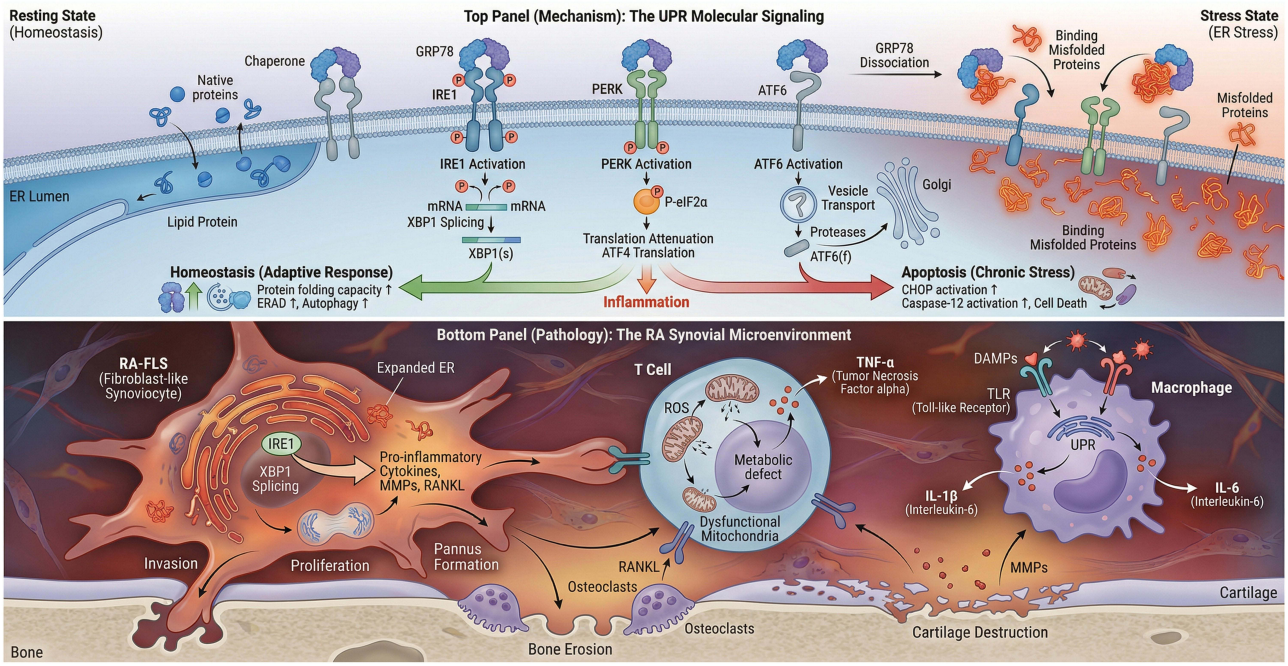

Figure 1 ER stress–activated UPR signaling and its pathogenic roles in rheumatoid arthritis. Top panel: Dissociation of GRP78/BiP under endoplasmic reticulum stress activates the three canonical UPR sensors—IRE1α, PERK, and ATF6—initiating adaptive programs that enhance protein folding, ER-associated degradation (ERAD), and translational attenuation. Sustained or unresolved stress shifts signaling toward inflammatory amplification and pro-apoptotic pathways. Bottom panel: Within the rheumatoid arthritis synovial microenvironment, persistent UPR activation in fibroblast-like synoviocytes and immune cells promotes pro-inflammatory cytokine production, metabolic reprogramming, pannus formation, osteoclast activation, and progressive cartilage and bone destruction.

Functional Modules of ER Stress Signaling in RA

Building upon the interconnected nature of IRE1α, PERK, and ATF6 signaling described above, accumulating evidence suggests that ER stress in RA operates through functionally distinct yet coordinated modules that extend beyond protein-folding control.[25] Rather than acting as isolated pathways, these modules integrate proteostatic regulation with inflammatory signaling, metabolic adaptation, and cell fate determination, providing a dynamic framework for understanding the context-dependent roles of ER stress during disease progression (Figure 1).

The proteostasis restoration module represents the canonical adaptive arm of the UPR, primarily mediated by GRP78 induction, ATF6 activation, and XBP1s-driven transcriptional programs.[26] This module enhances chaperone production, ER-associated degradation (ERAD), and folding capacity, thereby limiting misfolded protein accumulation. Under early or transient stress conditions in the RA synovium, it may exert cytoprotective effects and help restrain excessive inflammatory activation.[11]

Persistent IRE1α activation, particularly through its kinase and RNase activities, links ER stress to inflammatory signaling networks.[27] The IRE1–TRAF2–JNK axis and IRE1-dependent modulation of NF-κB pathways promote production of pro-inflammatory cytokines, including TNF-α and IL-6.[28] In macrophages and fibroblast-like synoviocytes (FLS), this inflammatory amplification module sustains synovial hyperactivation, while crosstalk with inflammasome signaling further connects ER dysfunction with innate immune responses.[29]

ER stress also interfaces with cellular metabolism. The PERK–ATF4 pathway regulates amino acid metabolism, redox homeostasis, and mitochondrial function, whereas XBP1s supports lipid biosynthesis and secretory expansion.[30] Within the hypoxic and nutrient-stressed RA synovial microenvironment, ER stress–driven metabolic reprogramming may facilitate abnormal FLS proliferation, apoptosis resistance, and invasive behavior, thereby reinforcing pathological remodeling.[9]

Under unresolved or excessive stress, signaling shifts toward a pro-apoptotic checkpoint module. PERK–ATF4–CHOP activation induces pro-apoptotic genes and modulates Bcl-2 family members, while sustained IRE1 activity may enhance JNK-mediated cell death pathways.[31] Notably, RA synovial tissue often exhibits apoptosis resistance rather than

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excessive cell loss, suggesting dysregulation of this checkpoint.[32] An imbalance between adaptive signaling and apoptotic execution likely contributes to persistent synovial hyperplasia and pannus formation.[33]

Collectively, ER stress in RA should be viewed not as a uniform stress response but as a context-dependent network in which discrete modules are selectively engaged according to stress intensity, duration, and cellular identity. Mild or transient stress preferentially activates proteostasis restoration, whereas chronic or high-intensity stress favors inflammatory amplification and metabolic rewiring. Impaired engagement of the apoptotic checkpoint further permits survival of pathogenic synovial cells, reinforcing disease persistence.

Stage-Dependent Roles of ER Stress in RA Progression

Early Adaptive ER Stress

During early rheumatoid arthritis or transient inflammatory flares, ER stress activation may exert predominantly adaptive and cytoprotective effects.[14] Synovial hypoxia, cytokine exposure, and metabolic perturbations impose a proteostatic burden on resident cells; however, moderate UPR activation enhances chaperone expression, transiently suppresses global protein translation, and restores ER homeostasis.[21]

In this adaptive phase, GRP78 upregulation and ATF6 activation strengthen protein-folding capacity and ER-associated degradation (ERAD), while controlled PERK–eIF2α signaling attenuates protein synthesis to limit misfolded protein accumulation and metabolic stress.[34,35] ER stress responses also intersect with antioxidant signaling and autophagy pathways, thereby supporting cellular survival under hypoxic and inflammatory conditions.[36,37] Within this context, early ER stress activation should be regarded not solely as a pathogenic trigger, but as a compensatory mechanism that buffers microenvironmental stress and helps restrain uncontrolled inflammatory escalation (Figure 1).

Chronic Maladaptive ER Stress

Under persistent inflammation and sustained exposure to hypoxia and oxidative stress, ER stress signaling may surpass adaptive capacity and transition into a maladaptive state.[38] This shift represents a pivotal inflection point in RA progression (Figure 1).

Prolonged IRE1α activation enhances JNK signaling and potentiates NF-κB–driven inflammatory amplification, sustaining production of TNF-α, IL-6, and related cytokines.[39] Concurrently, dysregulated PERK–ATF4–CHOP signaling may alter apoptotic thresholds.[38,40] Rather than facilitating effective clearance of pathogenic cells, incomplete or imbalanced activation of apoptotic programs can paradoxically promote apoptosis resistance in FLS, permitting expansion of aggressive and invasive cell populations.[9,41]

Chronic ER stress also drives metabolic reprogramming. XBP1s-dependent lipid biosynthesis and PERK-mediated redox adaptation support abnormal FLS proliferation, secretory expansion, pannus formation, and extracellular matrix degradation.[11,15] In macrophages and T cells, sustained ER stress skews cytokine production and T-cell differentiation, further destabilizing immune homeostasis.[42] Collectively, persistent ER stress transforms from a compensatory mechanism into a driver of inflammatory amplification, metabolic adaptation, and structural joint remodeling.

Determinants of the Adaptive-to-Maladaptive Transition

The transition of ER stress signaling from adaptive compensation to pathogenic remodeling in RA is governed by stress intensity, duration, cellular context, and inter-organelle communication.[43] Mild and transient ER perturbations preferentially activate proteostasis-restoring programs, whereas prolonged or high-intensity stress sustains inflammatory amplification and metabolic reprogramming.[44]

Cell type–specific thresholds further shape this transition. Distinct synovial populations exhibit differential sensitivity to ER stress: macrophages tend to amplify inflammatory cascades, whereas FLS more prominently display dysregulated apoptotic checkpoint control and survival signaling.[45] ER stress is also reinforced by mitochondrial dysfunction, reactive oxygen species accumulation, calcium imbalance, autophagy pathways, and inflammasome activation, forming interconnected stress circuits under chronic inflammatory conditions.[44,46]

Although induction of pro-apoptotic mediators such as CHOP represents a classical outcome of unresolved ER stress, incomplete execution of downstream apoptotic programs in RA synovium may permit persistence and expansion of pathogenic cell subsets.[47] Together, these determinants define a regulatory tipping point at which ER stress shifts from a cytoprotective buffering mechanism to a driver of inflammatory amplification and structural joint damage.

Cell-Type–Specific ER Stress Signaling in RA

ER stress in RA is not uniformly activated across the synovial microenvironment but exhibits pronounced cell type–specific characteristics. Distinct cellular populations, including FLS, macrophages, T cells, and osteoclasts, engage different UPR modules and downstream effector programs, leading to heterogeneous functional outcomes.[13,34] Rather than functioning as a generalized stress response, ER stress in RA operates as a lineage-dependent signaling platform that reshapes inflammatory output, metabolic adaptation, survival thresholds, and tissue-destructive capacity (Figure 2).

Fibroblast-Like Synoviocytes: ER Stress–Driven Survival and Inflammatory Reprogramming

RA-FLS exist under sustained proteostatic pressure within the inflamed synovium and characteristically translate ER stress signaling into proliferation-supporting and inflammatory programs rather than terminal apoptosis.[41,47] Transcriptomic and functional studies demonstrate enrichment of ER stress–associated gene signatures in RA synovium and increased GRP78/BiP expression in cytokine-stimulated RA-FLS. Functional modulation experiments further show that GRP78 supports TNF- or TGF-β–induced proliferation and angiogenic behavior, whereas GRP78 silencing enhances apoptosis and attenuates synovial hyperplasia in experimental arthritis models.[48,49] These findings establish ER stress in FLS as a survival-supporting module rather than a purely pro-apoptotic pathway.

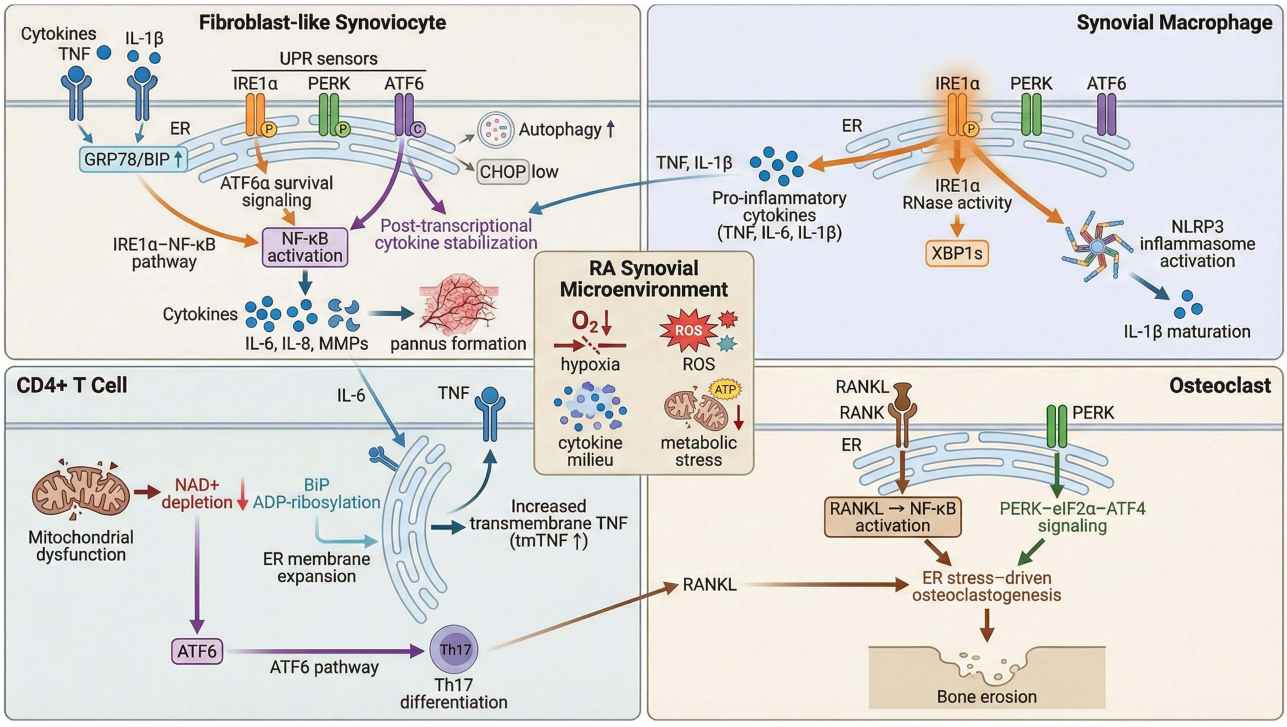

Figure 2 Cell-type–specific ER stress modules coordinate inflammation, immune skewing, and bone erosion in rheumatoid arthritis synovium. Fibroblast-like synoviocytes preferentially engage ATF6α-driven survival programs and IRE1α–NF-κB signaling, promoting cytokine production, matrix degradation, and pannus formation. Synovial macrophages predominantly activate the IRE1α–XBP1 axis, amplifying pro-inflammatory cytokine expression and NLRP3 inflammasome activation. In $CD4^+$ T cells, mitochondrial dysfunction induces ER membrane expansion and enhanced transmembrane TNF biogenesis, while ATF6 signaling contributes to Th17 differentiation. Osteoclasts integrate RANKL–NF-κB activation with PERK–eIF2α–ATF4 signaling to drive osteoclastogenesis and bone resorption. Thin arrows denote intercellular crosstalk within the synovial microenvironment. Collectively, these cell-specific modules illustrate how ER stress signaling is selectively rewired across synovial lineages to sustain chronic inflammation and progressive structural joint damage.

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Mechanistically, RA-FLS preferentially engage selective UPR branches. TNF stimulation increases phosphorylated eIF2α, cleaved ATF6, and GRP78, while CHOP induction remains limited, suggesting activation of a survival-biased ER stress program.[10] Among the UPR sensors, ATF6α has emerged as an important regulator in RA-FLS. ATF6α expression is elevated in patient-derived FLS, inducible by TNF-α and IL-1β, and required for proliferation and inflammatory mediator production.[50] Genetic silencing or pharmacological inhibition of ATF6α reduces IL-6, IL-23A, CXCL8, MMP1, and MMP13 expression, promotes apoptosis through modulation of Bcl-2 family proteins, and ameliorates arthritis severity in vivo.[51]

ER stress in FLS also cooperates with innate danger-sensing pathways. ER stress synergizes with TLR ligation to amplify inflammatory cytokine production, partly by increasing cytokine mRNA stability.[52,53] Consistently, XBP1 silencing attenuates ER stress–augmented IL-6, IL-8, TNF-α, MMPs, and VEGF expression, highlighting the IRE1–XBP1 axis as a key contributor to stromal inflammatory amplification.[54]

Apoptotic checkpoint dysregulation represents another defining feature of RA-FLS. Compared with osteoarthritis fibroblasts, RA-FLS exhibit reduced CHOP induction under ER stress and enhanced autophagy activation. Inhibition of autophagy restores ER stress–induced cell death, indicating that stress-adaptive autophagy contributes to apoptosis resistance.[32,55] Additionally, the ER-resident E3 ubiquitin ligase synoviolin (SYVN1) promotes ubiquitination and degradation of IRE1, selectively dampening pro-apoptotic signaling while preserving proliferative capacity.[56] Collectively, ER stress signaling in RA-FLS is rewired to sustain survival, invasion, angiogenesis, and inflammatory amplification, thereby driving pathogenic transformation rather than effective elimination.

Macrophages: ER Stress–Mediated Inflammatory Amplification

Synovial macrophages are a principal source of TNF-α, IL-6, and IL-1β in RA and display a distinct inflammatory UPR signature. Elevated levels of spliced XBP1 have been detected in RA synovial macrophages, consistent with enhanced IRE1α RNase activity.[57] Myeloid-specific deletion of IRE1α markedly reduces arthritis severity in experimental models, establishing a causal role for IRE1 signaling in disease amplification.[58]

Functionally, IRE1α deficiency attenuates TLR-induced production of IL-1β, IL-6, and TNF-α without compromising macrophage viability, indicating that ER stress acts upstream of canonical inflammatory transcriptional programs.[59,60] ER stress also intersects with inflammasome activation: sustained UPR signaling and reactive oxygen species (ROS) accumulation promote NLRP3 inflammasome assembly and IL-1β maturation, linking proteostatic imbalance to innate immune effector activation.[34,61]

In contrast to FLS, macrophages predominantly engage inflammatory amplification modules rather than apoptosis resistance pathways. Within this lineage, the IRE1α–XBP1 axis functions as a gain-control node that stabilizes cytokine output and perpetuates chronic synovial inflammation.[62]

T Cells: Metabolic–ER Crosstalk and Effector Reprogramming

In RA T cells, ER stress activation is closely coupled to metabolic and mitochondrial dysfunction rather than classical proteotoxic stress alone. Impaired mitochondrial aspartate production has emerged as a key abnormality in RA T cells.[63] Reduced aspartate availability limits NAD regeneration, promotes ADP-ribosylation of GRP78/BiP, and induces expansion of ribosome-rich ER membranes.[64] This ER remodeling enhances co-translational translocation and increases transmembrane TNF biogenesis, rendering ER-expanded T cells potent TNF producers within the arthritic joint.[65] Restoration of mitochondrial function or aspartate supplementation reduces ER expansion and TNF production, underscoring the metabolic dependency of T-cell ER stress responses.[63] Together, these findings position GRP78/BiP as a mitochondria-regulated ER stress switch and highlight ER–mitochondrial communication as a determinant of inflammatory effector output.[66]

In parallel, ATF6 signaling contributes to Th17 differentiation. ATF6α regulates transcriptional programs associated with STAT3 and RORC, whereas pharmacological inhibition attenuates Th17 polarization in experimental systems.[50] Collectively, ER stress signaling in T cells functions as a metabolic and differentiation checkpoint, shaping effector bias and immune imbalance in RA.

Osteoclasts: ER Stress–Driven Osteoclastogenesis and Bone Resorption

Excessive osteoclast differentiation and bone resorption are central drivers of joint erosion in RA. ER stress is activated during RANKL-induced osteoclastogenesis and interfaces with NF-κB–dependent differentiation programs.[6]

The PERK–eIF2α–ATF4 axis supports osteoclast maturation, particularly under oxidative stress. Pharmacological modulation of ER stress attenuates RANKL-induced osteoclast formation and reduces bone-resorptive activity.[6,67] In collagen-induced arthritis models, salubrinal decreases arthritis severity, suppresses NF-κB signaling, promotes p65 degradation, reduces osteoclast numbers, and limits bone erosion.[68] These findings indicate that ER stress functions as a differentiation and effector amplifier in osteoclasts, integrating inflammatory cues with bone-destructive capacity.

Intercellular Crosstalk and Microenvironmental Integration

While the roles of individual cell types have been described above, ER stress in RA also operates through dynamic intercellular crosstalk across the synovial microenvironment.[47] ER stress–activated macrophages produce pro-inflammatory cytokines such as TNF-α and IL-6 through the IRE1α–XBP1[69] and NF-κB[70] pathways. These cytokines act in a paracrine manner on FLS, where they increase protein synthesis demand, disrupt intracellular calcium homeostasis, and promote ROS accumulation, leading to misfolded protein accumulation and activation of PERK–eIF2α and ATF6 signaling. This establishes a feed-forward inflammatory circuit that amplifies synovial activation.

In turn, ER stress–activated FLS secrete inflammatory and osteoclastogenic mediators such as IL-6 and RANKL.[71] Mechanistically, IL-6 activates the JAK–STAT3 pathway in T cells, promoting Th17 differentiation, whereas RANKL engages RANK–NF-κB signaling in osteoclast precursors, driving osteoclastogenesis and bone resorption.[72,73] Additionally, ER stress–induced mitochondrial dysfunction promotes ROS generation and calcium flux, which can propagate via extracellular vesicles or paracrine signaling to reinforce ER stress responses in neighboring immune and stromal cells.[6]

Collectively, these observations indicate that ER stress propagation in RA is mediated not only by cytokine signaling but also by metabolic perturbation and organelle stress coupling across different cell populations. This establishes a self-reinforcing intercellular network in which ER stress is transmitted and amplified across the synovial microenvironment, ultimately sustaining chronic inflammation and structural joint damage.

Integrative Signaling Functions of ER Stress in RA

ER stress in rheumatoid arthritis should not be viewed as an isolated intracellular response but as an integrative signaling hub that coordinates inflammatory signaling, metabolic reprogramming, and cell fate control within the synovial microenvironment (Figure 3). Experimental arthritis models and analyses of RA synovial tissue reveal concurrent activation of multiple stress-responsive pathways, indicating that UPR branches dynamically interface with inflammatory and metabolic circuits.[52,74]

ER Stress and NF-κB–Driven Inflammatory Networks

A prominent point of convergence lies between ER stress and NF-κB signaling. In collagen-induced arthritis (CIA) models and cultured RA-FLS, IRE1α activation recruits TRAF2, leading to JNK phosphorylation and activation of the IKK complex, thereby enhancing NF-κB–dependent transcription of TNF-α, IL-6, and MMPs.[75] Pharmacological inhibition of IRE1 RNase activity attenuates NF-κB nuclear translocation and cytokine production, supporting a causal role for UPR signaling in inflammatory amplification.[76]

Inflammatory cytokines, including TNF-α and IL-1β, reciprocally increase intracellular calcium flux and proteostatic burden, promoting PERK and IRE1 phosphorylation in synovial cells.[77] This establishes a bidirectional feedback circuit in which ER stress both responds to and reinforces inflammatory signaling, thereby contributing to persistence of chronic inflammation within the RA synovium.

Crosstalk Between ER Stress and Autophagy

Autophagy constitutes a critical adaptive mechanism that closely interfaces with ER stress signaling.[78] In RA-FLS and macrophages, activation of the PERK–eIF2α–ATF4 axis induces autophagy-related genes, including LC3 and ATG

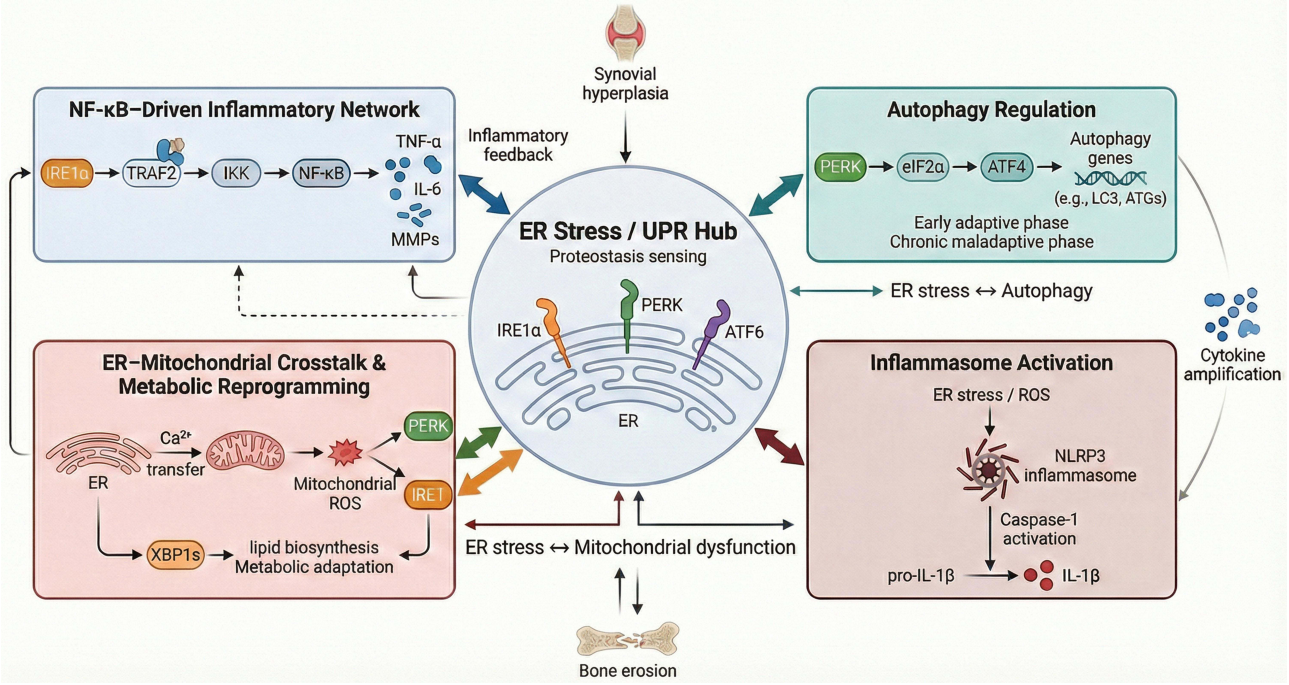

Figure 3 ER stress as an integrative signaling hub in rheumatoid arthritis. ER stress functions as a central regulatory hub within the rheumatoid arthritis synovial microenvironment, integrating inflammatory signaling, metabolic reprogramming, autophagic regulation, and inflammasome activation. Activation of IRE1α links ER stress to NF-κB–driven cytokine production, whereas PERK signaling interfaces with autophagy and mitochondrial bioenergetics. ER–mitochondrial crosstalk enhances ROS generation and metabolic adaptation, reinforcing stress signaling circuits. Persistent proteostatic imbalance further promotes NLRP3 inflammasome assembly and IL-1β maturation. Collectively, this interconnected network architecture positions ER stress as an active amplifier of chronic inflammation and structural joint damage rather than a linear downstream consequence.

family members,[10,79] while the IRE1α–JNK axis also contributes to ER stress–induced autophagy in synovial cells.[80] Through these coordinated pathways, autophagy facilitates the clearance of misfolded proteins and damaged organelles, thereby alleviating proteotoxic and oxidative stress.

This ER stress–autophagy coupling exhibits context-dependent effects. Under transient or moderate stress, autophagy acts as a compensatory mechanism to reduce proteotoxic burden, remove damaged organelles, and restrain excessive inflammatory activation.[81] However, in chronically inflamed RA synovium, sustained activation of autophagy becomes maladaptive, supporting the survival of pathogenic FLS and promoting apoptosis resistance. Indeed, enhanced autophagy is associated with reduced ER stress–induced cell death in RA-FLS, whereas inhibition of autophagy restores apoptotic sensitivity under unresolved stress conditions.

In addition to this functional duality, dysregulation of autophagic flux further contributes to disease progression. Chronic inflammatory exposure can impair autophagic flux, resulting in the accumulation of dysfunctional mitochondria and sustained ROS production.[82] In CIA models, defective autophagy correlates with elevated GRP78 and CHOP expression, indicating failure of stress resolution mechanisms.[8,83] Restoration of autophagic activity reduces ER stress markers and attenuates inflammatory cytokine output, supporting the concept that ER stress–autophagy imbalance contributes to maladaptive remodeling in RA.

ER–Mitochondrial Crosstalk and Metabolic Reprogramming

The endoplasmic reticulum and mitochondria are structurally and functionally coupled through mitochondria-associated membranes (MAMs), which coordinate calcium transfer and lipid exchange.[84] In RA synovial tissue, mitochondrial dysfunction, characterized by impaired oxidative phosphorylation and increased ROS production, coexists with elevated ER stress markers.[85]

Excessive calcium transfer from the ER to mitochondria amplifies mitochondrial ROS generation, which further activates PERK and IRE1 signaling, forming a self-reinforcing stress circuit.[86] PERK-mediated pathways influence mitochondrial bioenergetics and redox balance,[87] whereas XBP1s-driven lipid biosynthesis supports membrane expansion and secretory activity in hyperactive FLS.

Experimental modulation of mitochondrial ROS attenuates ER stress activation and reduces inflammatory gene expression, underscoring the functional coupling between these organelles.[88,89] Through this ER–mitochondrial interplay, proteostatic disturbance is linked to metabolic dysfunction and inflammatory amplification in RA.

ER Stress and Inflammasome Activation

ER stress has been increasingly implicated in activation of inflammasomes, particularly NLRP3.[90] Sustained UPR signaling and ROS accumulation promote assembly of NLRP3 inflammasome complexes in macrophages, leading to caspase-1 activation and maturation of IL-1β.[91] In experimental arthritis models, attenuation of ER stress reduces IL-1β secretion and alleviates synovial inflammation,[92] indicating that proteostatic imbalance contributes to innate immune activation. The convergence of ER stress, mitochondrial dysfunction, and inflammasome signaling further reinforces chronic inflammatory circuits in RA.

Collectively, evidence from synovial tissue analyses, in vitro cellular systems, and experimental arthritis models supports the view that ER stress in RA functions as a dynamic signaling hub rather than a linear cascade. Through interactions with NF-κB–driven inflammatory circuits, autophagic regulation, mitochondrial metabolism, and inflammasome activation, ER stress integrates environmental stress cues with immune dysregulation and structural joint damage.

This network architecture may help explain why global ER stress inhibition can produce inconsistent outcomes. Broad suppression may disrupt adaptive proteostasis modules, whereas selective targeting of discrete nodes, such as IRE1-mediated inflammatory amplification or PERK-dependent survival signaling, may interrupt pathogenic feedback loops while preserving essential homeostatic functions.

Precision Pharmacological Modulation of ER Stress in Rheumatoid Arthritis

Given the stage-dependent and cell type–specific roles of ER stress in RA, therapeutic strategies should avoid indiscriminate suppression or activation of the UPR. Instead, pharmacological interventions may be conceptualized according to their effects on discrete ER stress modules within the inflammatory microenvironment. Current evidence supports three principal paradigms: (i) attenuation of excessive proteostatic burden, (ii) selective induction of pro-apoptotic ER stress in pathogenic cells, and (iii) node-specific targeting within inflammatory UPR networks (Table 1).

Attenuation of Excessive ER Stress: Restoring Adaptive Homeostasis

In early or inflammation-dominant phases of RA, excessive proteostatic and oxidative stress may drive maladaptive inflammatory amplification.[104] In this setting, pharmacological attenuation of ER stress aims to restore adaptive homeostasis rather than eliminate pathogenic cells.

Chemical chaperones such as 4-phenylbutyric acid (4-PBA) enhance ER protein-folding capacity, reduce accumulation of misfolded proteins, and suppress excessive UPR activation.[105] In CIA models, 4-PBA alleviates joint swelling, bone erosion, and inflammatory mediator production.[92] Similarly, salubrinal, an inhibitor of eIF2α dephosphorylation, sustains controlled PERK signaling and reduces osteoclastogenesis and inflammatory bone destruction.[93,94]

Several multi-target bioactive compounds, including tanshinone IIA,[95] paeoniflorin,[96] and baicalin,[97] also modulate ER stress pathways by attenuating overactivation of GRP78, IRE1α, XBP1, and CHOP, thereby dampening inflammatory cascades and oxidative stress. Rather than acting solely as anti-inflammatory agents, they may recalibrate proteostatic and metabolic balance within synovial cells.

Conceptually, such strategies are most applicable to early-stage or inflammation-dominant disease. However, global attenuation of ER stress may impair protective adaptive responses; thus, temporal precision and dosage optimization remain critical considerations.

Table 1 Pharmacological and Translational Strategies Modulating ER Stress Pathways in Rheumatoid Arthritis

Functional Module	Agent/Strategy	Primary ER Stress Target	Experimental Model	Major Reported Effects in RA	Ref.
Attenuation of excessive ER stress	4-PBA	Chemical chaperone; ↓ GRP78, CHOP; reduces UPR overactivation	CIA model; RA-FLS	↓ joint swelling; ↓ bone erosion; ↓ inflammatory cytokines	92
Repurposed drugs	Salubrinal	Maintains eIF2α phosphorylation (PERK pathway modulation)	CIA model	↓osteoclastogenesis; ↓ inflammatory bone destruction	93,94
	Tanshinone IIA	↓ GRP78, IRE1α/XBP1 signaling	CIA model	↓ synovial inflammation; ↓ oxidative stress	95
	Paeoniflorin	Modulates PERK and IRE1 pathways	CIA model	↓ inflammatory mediator production	96
	Baicalin	↓ CHOP expression; antioxidant effects	CIA model; RA-FLS	↓ apoptosis imbalance; ↓ inflammatory signaling	97
Selective activation of pro-apoptotic ER stress	Oridonin	Activates PERK–eIF2α–CHOP axis	CIA model; RA-FLS	↑ apoptosis of RA-FLS; ↓ synovial hyperplasia	12
	Docosahexaenoic acid (DHA)	Induces CHOP and DR5 expression	RA-FLS	↑ caspase-dependent apoptosis	98
	Daphnetin	Activates PERK–ATF4 signaling; ↓ Bcl-2	CIA model	↑ apoptosis of pathogenic FLS; ↓ inflammation	99
Node-specific inflammatory UPR modulation	Azithromycin	Context-dependent UPR modulation; affects IRE1/XBP1	CIA model; osteoclast precursors	↓ osteoclast differentiation; ↓ inflammatory cytokines	100
	Tacrolimus	↓ PERK, IRE1, ATF6 overactivation	CIA model	↓ inflammatory infiltration; ↓ osteoclast formation	101
Cell-specific delivery systems	FAP-targeted iron–zinc nanoparticles (FAP-ZF-NPs)	Local activation of PERK–ATF4–CHOP and IRE1–XBP1 in RA-FLS	CIA model	Selective induction of synoviocyte apoptosis; reduced systemic toxicity	102
Clinical ER-homeostasis modulation	Triple csDMARD therapy: methotrexate, sulfasalazine, and hydroxychloroquine	XBP1-associated secretory program	Paired synovial biopsies from early RA patients	Downregulated XBP1-associated secretory programs, suggesting indirect modulation of ER-homeostasis networks in early RA synovium	103

Selective Activation of Pro-Apoptotic ER Stress in Pathogenic Synoviocytes

In established RA characterized by hyperproliferative and apoptosis-resistant FLS,[106] therapeutic priorities may shift from stress attenuation to selective elimination of pathogenic stromal subsets. In this setting, deliberate activation of pro-apoptotic ER stress modules may help restore apoptotic checkpoint control.

Oridonin activates the PERK–eIF2α–CHOP axis and induces apoptosis in RA-FLS.[12] Docosahexaenoic acid (DHA) triggers robust ER stress marked by CHOP and death receptor 5 (DR5) upregulation, leading to caspase-dependent cell death.[98] Daphnetin similarly enhances PERK–ATF4 signaling while suppressing anti-apoptotic proteins such as Bcl-2.[99]

These interventions may drive dysregulated synoviocytes beyond their adaptive capacity, promoting apoptosis in hyperactive stromal populations. However, systemic induction of ER stress carries potential toxicity risks; therefore, tissue-specific delivery and dose optimization are critical considerations for translational application.

Node-Specific Modulation of Inflammatory UPR Signaling

Given the central role of the IRE1–XBP1 axis in inflammatory amplification, selective modulation of this pathway represents a rational therapeutic approach. Inhibition of IRE1 RNase activity attenuates cytokine production and may rebalance Th17/Treg differentiation without fully disrupting adaptive proteostasis.[107]

Several agents further illustrate the context-dependent nature of inflammatory UPR modulation. Azithromycin can activate UPR signaling to induce apoptosis in RA-FLS while concurrently suppressing inflammatory mediator production.[100] Tacrolimus has been reported to attenuate excessive activation of PERK, IRE1, and ATF6 pathways in arthritis models, thereby reducing inflammatory infiltration and osteoclastogenesis.[101]

These observations underscore the complexity of UPR targeting, where therapeutic benefit may arise from calibrated modulation of signaling intensity rather than uniform pathway inhibition. Targeting specific interfaces, such as ER stress–NF-κB or ER stress–JNK crosstalk, may further enhance precision by interrupting inflammatory amplification loops while preserving essential adaptive functions.

Cell-Specific Delivery and Technological Innovations

A major translational challenge of ER stress modulation lies in achieving cell- and tissue-specific targeting. Advances in nanotechnology may offer potential solutions to this limitation. Fibroblast activation protein (FAP)–targeted iron–zinc nanoparticles (FAP-ZF-NPs) have been reported to preferentially accumulate in RA-FLS–rich synovial lesions and induce localized activation of PERK–ATF4–CHOP and IRE1–XBP1 pathways, thereby promoting apoptosis while limiting systemic exposure.[102] Magnetothermal enhancement strategies may further enable spatial and temporal control of ER stress activation.[108] Such approaches align with stage-dependent therapeutic logic, permitting selective elimination of pathogenic stromal populations without broadly compromising systemic immune function.

Translational Integration of ER Stress Modulation in RA

Several clinically used RA therapies intersect with ER-homeostasis pathways; however, direct clinical evidence supporting ER stress as an actionable therapeutic target in RA remains limited. A key RA-specific human signal comes from paired synovial-biopsy transcriptomic evidence showing that triple conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy, consisting of methotrexate, sulfasalazine, and hydroxychloroquine, downregulates XBP1-associated secretory programs in early RA synovium.[103] In contrast, most approved RA therapies appear to modulate ER stress indirectly or in a context-dependent manner. JAK inhibitors, represented by tofacitinib, may indirectly modulate ER stress by reducing inflammatory and oxidative burden and improving cellular metabolic homeostasis.[109,110] Accordingly, these therapies are best regarded as indirect or context-dependent modulators of ER-stress pathways rather than validated ER-stress-targeting agents.

Collectively, current pharmacological evidence suggests that ER stress modulation in RA should be approached as precision recalibration of a dynamic regulatory network rather than uniform pathway inhibition. Early inflammatory phases may benefit from attenuation of excessive proteostatic and inflammatory burden to restore adaptive balance, whereas advanced disease characterized by synovial hyperplasia may require strategies that restore apoptotic sensitivity or selectively disrupt maladaptive stress-adaptive programs in pathogenic cell populations. Modulation of stress–inflammatory nodes, such as the IRE1–XBP1 axis, may help rebalance immune dysregulation while preserving essential homeostatic functions. These considerations highlight the importance of stage- and cell-specific ER stress responses in RA. Rather than conceptualizing ER stress as a uniform therapeutic target, effective intervention will likely depend on context-dependent strategies aligned with disease stage, cellular phenotype, and the dynamic progression of synovial pathology.

Conclusion and Future Perspectives

Evidence accumulated over the past decade establishes ER stress as an important component of rheumatoid arthritis pathogenesis, extending beyond its canonical role in proteostasis maintenance. Rather than representing a passive byproduct of inflammation, ER stress integrates microenvironmental stress, immune signaling, metabolic

reprogramming, and structural joint remodeling. Viewing ER stress through a stage-dependent and cell type–specific lens helps reconcile its seemingly paradoxical roles during RA progression.

In early inflammatory phases, adaptive UPR activation may buffer proteostatic burden and preserve cellular homeostasis. With persistent or dysregulated activation, however, ER stress signaling shifts toward inflammatory amplification, metabolic rewiring, apoptosis resistance in fibroblast-like synoviocytes, immune imbalance, and enhanced osteoclastogenesis. This adaptive-to-maladaptive transition represents a critical inflection point in disease evolution and supports contextual modulation rather than uniform pathway inhibition.

Despite substantial mechanistic advances, key challenges remain. The temporal dynamics of ER stress activation across disease stages require more precise characterization, ideally through longitudinal and single-cell–resolved analyses. The thresholds governing the switch from cytoprotective to pathogenic UPR signaling remain incompletely defined. Reliable biomarkers reflecting cell-specific ER stress activation states are also lacking, limiting clinical translation. Moreover, most therapeutic evidence derives from preclinical models, and the safety, specificity, and long-term consequences of ER stress modulation in humans require rigorous evaluation.

Future research should integrate multi-omics platforms, spatial transcriptomics, and advanced imaging approaches to map ER stress activity across cellular subsets within the RA synovium. Development of synovium-targeted delivery systems and stage-adapted intervention strategies may enable precision recalibration of ER stress signaling while preserving systemic immune competence. Rational combination regimens incorporating ER stress modulation with established biologic or small-molecule therapies also warrant exploration, particularly in treatment-refractory disease.

In summary, reframing ER stress as a dynamic and context-dependent signaling network reshapes our understanding of RA pathogenesis and identifies new avenues for therapeutic innovation. Precision modulation guided by disease stage, cellular identity, and network-level integration may ultimately transform ER stress from a mechanistic insight into a clinically actionable target.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Author Contributions

Na Hu: Conceptualization, Investigation, Writing – original draft, Writing – review and editing; Yaguang Song: Investigation, Data Curation, Writing - Review & Editing; Ting Yu: Visualization, Writing - Review & Editing; Hongbo Li: Visualization, Writing - Review & Editing; Xin Wang: Visualization, Writing - Review & Editing; Qingguo Lv: Conceptualization, Supervision, Project Administration, Writing - Review & Editing. All authors have approved the final version of the article, agreed on the journal to which the article was submitted, and agree to be accountable for all aspects of the work.

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