

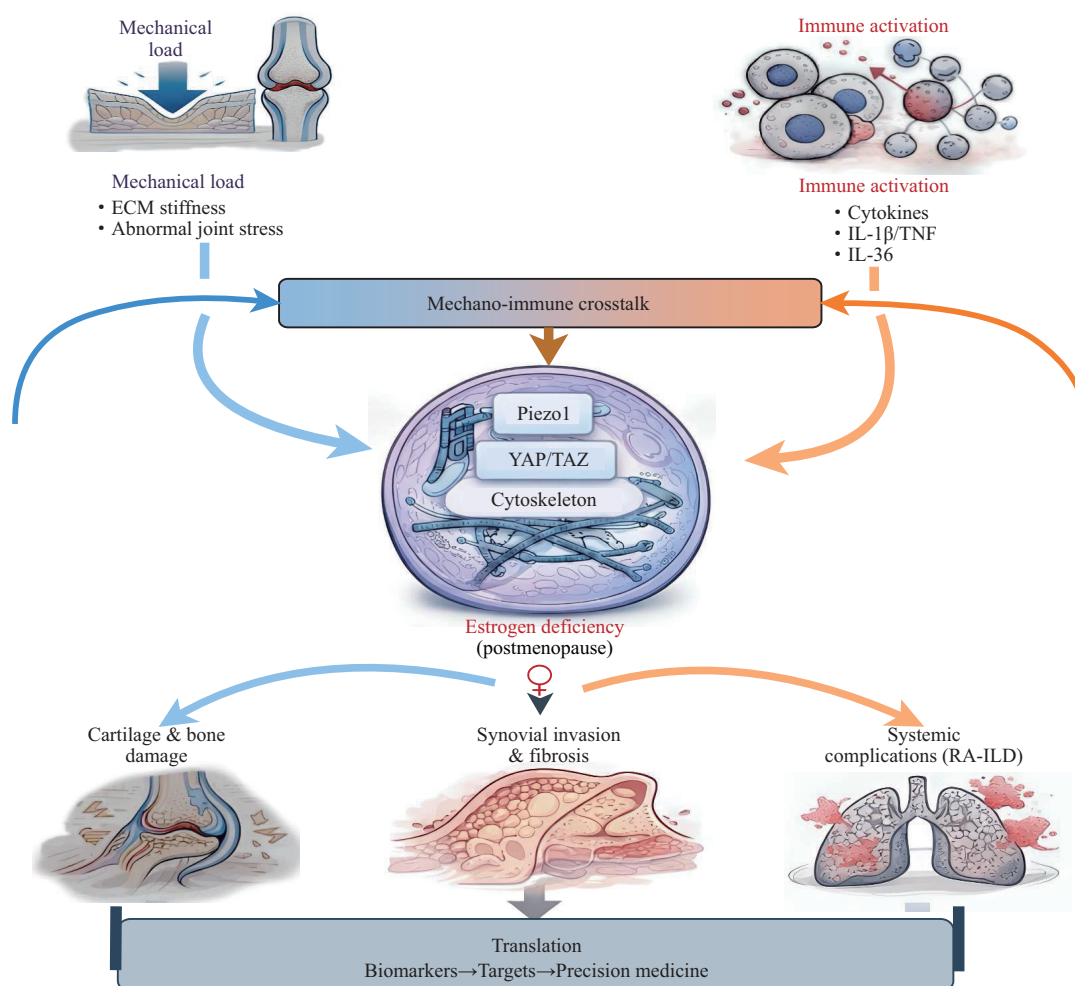


Mechano-immune Crosstalk in Osteoarthritis and Rheumatoid Arthritis: Cytoskeletal and Mechanotransductive Biomarkers and Translational Therapeutic Targets in Postmenopausal Disease

ABOD Kareem Salim*, ABBAS Salma Abdulredha

(Department of Chemistry, College of Science, Mustansiriyah University, Baghdad 10001, Iraq)

Graphical abstract



* Corresponding author.

Tel: 964-772-102-9309, E-mail: Kareemsalim113@uomustansiriyah.edu.iq

Received: October 30, 2025 Accepted: January 23, 2026

Abstract Osteoarthritis (OA) and rheumatoid arthritis (RA) have long been framed as degenerative and autoimmune entities, respectively; mounting evidence instead supports a unified mechano-immune paradigm in which joint loading and inflammatory signaling are reciprocally reinforcing. In this review, we synthesize advances across mechanotransduction (Piezo1; YAP/TAZ), focal-adhesion/cytoskeletal regulation (vinculin, filamin-A; upstream talin-1/Kindlin-2/paxillin), and niche inflammatory mediators (HE4, IL-36/IL-38) to explain how mechanical stress and cytokines co-produce persistent catabolism, synovial invasion, and fibrotic remodeling. We articulate a dual-hit model in which OA is predominantly mechanical-overload-driven, with secondary inflammation, whereas RA is immune-driven but imposes abnormal mechanical stress that further distorts joint biomechanics; both converge on canonical hubs (NF- κ B/MAPK/JAK-STAT) to accelerate matrix degradation and apoptosis. Building on this framework, we propose integrated multi-marker panels that combine mechanosensors and adhesion proteins with conventional assays (CRP, ESR, anti-CCP) to enhance differential diagnosis and prognostication, particularly in postmenopausal women, where estrogen decline heightens mechano-immune susceptibility, thereby offering a means to quantify the impact of mechano-immune dysregulation. Integrating mechanotransductive and cytoskeletal biomarkers with conventional serological indices has been reported to improve differential diagnosis between osteoarthritis and rheumatoid arthritis in exploratory studies. While the magnitude of diagnostic gain varies across cohorts, combined biomarker strategies generally show enhanced discriminatory performance compared with single-marker approaches. These findings highlight translational potential but require validation in large, standardized clinical populations before routine implementation. Finally, we map translational opportunities spanning Piezo1 inhibition (GsMTx4), YAP/TAZ blockade (verteporfin), IL-36 axis antagonism (IL-36Ra, IL-38), anti-HE4 strategies for RA-ILD, and adhesion-stabilizing approaches, alongside mechanoresponsive biomaterials for regenerative applications and precision medicine guided by biomarker profiles. Collectively, this review reframes OA and RA as mechano-immune syndromes and delineates a clinically actionable roadmap from biophysics to bedside.

Key words osteoarthritis, rheumatoid arthritis, cellular mechanotransduction, cytoskeleton, biomarkers, precision medicine, Piezo1, YAP/TAZ

DOI: 10.3724/j.pibb.2025.0475

CSTR: 32369.14.pibb.20250475

In mammals, cellular mechanotransduction and cytoskeletal integrity represent fundamental processes that maintain tissue homeostasis and orchestrate immune-mechanical crosstalk^[1]. Focal adhesion proteins—including vinculin, filamin-A, talin, Kindlin-2, and paxillin—link the extracellular matrix (ECM) with the actin cytoskeleton, thereby governing cell adhesion, migration, and signal transduction. Alongside these, mechanosensitive ion channels such as Piezo1 and transcriptional co-regulators such as YAP/TAZ translate physical forces into biochemical responses that shape chondrocyte survival, synovial fibroblast activation, and inflammatory cascades^[2-4]. In parallel, non-classical mediators such as human epididymis protein 4 (HE4) and interleukin-36 (IL-36) have emerged as novel contributors to joint pathology, linking fibrotic remodeling and cytokine-driven inflammation to cartilage degeneration, particularly in the postmenopausal setting^[5-6].

At its core, this review proposes that osteoarthritis (OA) and rheumatoid arthritis (RA) converge on a shared mechano-immune axis, in which mechanical loading, cytoskeletal remodeling, and inflammatory signaling are functionally inseparable rather than sequential events. Central mechanotransductive regulators—particularly Piezo1 and the YAP/TAZ transcriptional complex—emerge as molecular hubs that integrate ECM mechanics with

immune activation^[7-8]. This conceptual framework is especially relevant in postmenopausal disease, where estrogen deficiency lowers the threshold for mechano-immune dysregulation, reshaping disease initiation, progression, and translational opportunities^[9-10].

OA and RA are the most prevalent painful and disabling arthropathies worldwide. OA affects more than 250 million individuals globally, representing the leading cause of disability in older adults, while RA affects approximately 1% of the global population, imposing substantial socioeconomic and healthcare burdens^[11-12]. OA is primarily a degenerative disorder driven by senescence, obesity, trauma, and abnormal mechanical loading. In contrast, RA is an autoimmune disease characterized by synovial hyperplasia, autoantibody production, and chronic inflammation culminating in progressive joint destruction. Despite their distinct etiologies, both conditions share a common hallmark: irreversible cartilage and ECM degradation^[13-14].

Postmenopausal women represent a uniquely vulnerable population. The abrupt decline in estrogen after menopause accelerates bone loss, enhances oxidative stress, and amplifies inflammatory signaling, thereby worsening disease onset, severity, and outcomes in both RA and OA^[15-16]. Current diagnostic markers—such as C-reactive protein (CRP),

anti-citrullinated peptide antibodies (ACPA), and matrix metalloproteinases—remain limited in specificity and prognostic value, particularly for differentiating RA from OA in postmenopausal women. This underscores the urgent need for novel mechanotransduction-driven and cytoskeletal biomarkers that not only illuminate disease pathogenesis but also guide diagnosis, prognosis, and therapy^[17-18].

These findings indicate a molecular convergence with mechanotransduction pathways. Recent evidence implicates Wnt/ β -catenin signaling, m6A-modified long non-coding RNAs (lncRNAs), and liquid-liquid phase separation (LLPS) as upstream regulators that couple inflammatory cues to mechanical execution programs in joint tissues. In chondrocytes and synoviocytes, these dysregulated pathways interface with YAP/TAZ activity and focal-adhesion remodeling to reprogram transcription, amplify matrix catabolism, and sustain fibro-inflammatory niches—thereby providing a mechanistic bridge between canonical inflammatory signaling and Piezo1-driven force sensing in RA and OA^[2, 19-21].

In this review, we systematically synthesize the roles of nine emerging factors—HE4, vinculin, filamin-A, talin, Kindlin-2, paxillin, Piezo1, YAP/TAZ, and IL-36—in the context of postmenopausal RA and OA. Specifically, we aim to: (1) provide a comprehensive description of their molecular and structural characteristics and their integration into ECM-cytoskeleton networks; (2) analyze the mechanisms by which these biomarkers contribute to cartilage degradation, synovial inflammation, and joint damage in RA and OA; (3) evaluate their diagnostic and prognostic potential for disease differentiation in postmenopausal women; (4) explore their translational relevance as therapeutic targets and components of biomarker panels for precision medicine in arthritis.

To clarify the novelty of this synthesis in relation to existing literature, it is important to emphasize how the present review differs from prior studies. Unlike previous reviews that have addressed mechanotransduction, inflammatory signaling, or fibrotic remodeling in OA and RA largely as parallel or partially overlapping processes, the present work advances a unified mechano-immune framework in which mechanical loading, cytoskeletal remodeling, and immune activation are mechanistically inseparable. Rather than discussing Piezo1/YAP/TAZ signaling or inflammatory mediators in isolation, we integrate mechanosensors, focal-adhesion and cytoskeletal regulators, and niche mediators

(including HE4 and IL-36/IL-38) within shared intracellular convergence hubs (NF- κ B/MAPK/JAK-STAT) to explain divergent OA-RA disease trajectories. Importantly, this review uniquely centres on postmenopausal estrogen deficiency as a biological amplifier of mechano-immune susceptibility and extends these mechanistic insights toward clinically actionable biomarker-panel concepts and therapeutic prioritization strategies. Together, this integrative and translational perspective moves beyond descriptive synthesis and delineates a conceptual framework not explicitly developed in previous reviews.

1 Cytoskeletal and mechanotransduction biomarkers in postmenopausal arthritis

This section delineates the pathogenic mechanisms by which mechanical stress and inflammatory signaling drive cartilage damage in OA and RA. It contrasts OA, where abnormal mechanical loading predominates and promotes extracellular matrix breakdown through Piezo1 overactivation, Filamin-A dysregulation, and matrix-degrading enzymes, with RA, where immune-driven synovitis and invasive fibroblast-like synoviocytes orchestrate pannus formation and cartilage invasion. By integrating mechanotransductive regulators (Piezo1 and YAP/TAZ), adhesion signaling (talin, Kindlin-2, paxillin), and inflammatory mediators (HE4 and IL-36), this section highlights how distinct initiating triggers converge on shared execution pathways that culminate in cartilage destruction in postmenopausal joints.

1.1 Molecular structure and biological functions

Postmenopausal arthritis is characterized by altered biomechanics and persistent inflammation, which are sensed and mediated by specialized biomolecules. These molecules include cytoskeletal and focal adhesion proteins, mechanosensitive ion channels, transcriptional co-activators, and secreted inflammatory mediators. Collectively, they form an integrated network that couples ECM mechanics with intracellular signaling and gene regulation^[22-23].

Among focal adhesion proteins, vinculin, talin, filamin-A, Kindlin-2, and paxillin are pivotal in linking integrins to the actin cytoskeleton. Talin and Kindlin-2 initiate integrin activation, while vinculin and filamin-A reinforce adhesion under force by binding F-actin and transmembrane receptors in a tension-dependent manner. Paxillin functions as a scaffold that recruits kinases such as FAK and Src, thereby integrating mechanical and chemical signaling. Together, these proteins enable cells to

sense ECM stiffness and transduce it into biochemical pathways, as summarised in Table 1^[24-25].

Piezo1, a trimeric mechanosensitive ion channel, directly converts mechanical stretch or pressure into calcium influx, thereby activating downstream cascades such as MAPK and BMP signaling pathways. This process influences chondrocyte and synoviocyte responses to altered joint loading, a hallmark of OA and RA^[26]. At the nuclear level, YAP and TAZ, co-activators of the Hippo pathway, act as transcriptional mechanosensors. They shuttle to the nucleus under mechanical stress or matrix stiffening, driving gene expression programs linked to proliferation, matrix remodeling, and fibrosis^[27].

Secreted factors further shape the pathological milieu. HE4 (WFDC2) inhibits proteases and promotes collagen accumulation, thereby linking chronic inflammation to fibrosis and aberrant ECM remodeling^[28]. Elevated HE4 levels have been associated with more severe RA and systemic fibrotic complications in postmenopausal women^[29]. IL-36, a member of the IL-1 cytokine family, amplifies

synovial inflammation by activating NF- κ B and MAPK signaling, stimulating the release of pro-inflammatory mediators and matrix-degrading enzymes. Its enrichment in RA and psoriatic arthritis synovia underscores its contribution to chronic immune activation^[30-31].

Taken together, these biomarkers illustrate how cytoskeletal dynamics, mechanotransduction pathways, and inflammatory mediators converge to shape the pathophysiology of postmenopausal arthritis. Their dual roles in mechanical sensing and immune modulation highlight their potential as diagnostic and therapeutic targets in both RA and OA.

1.2 Regulatory mechanisms governing mechano-immune signaling

In joint homeostasis, cytoskeletal and focal-adhesion proteins, mechanosensors, and inflammatory mediators are governed by coordinated cycles of activation, post-translational modification (PTM), and degradation that tune adhesion dynamics, mechanosensitivity, and ECM remodeling. In postmenopausal arthritis, estrogen deficiency and the

Table 1 Structural and functional features of emerging mechanotransduction biomarkers in postmenopausal arthritis

Biomarker	Structural features	Core function	Role in RA/OA (postmenopausal)	Reference
Vinculin	116 ku, head-tail domains, binds talin & actin	Reinforces focal adhesions under tension	Strengthens integrin-actin linkage, stabilizes synovium	[32-33]
Filamin-A	280 ku dimer, 24 Ig-like repeats, actin-binding	Crosslinks actin, a mechanosensor	Responds to matrix stiffness, regulates signaling	[34]
Talin	270 ku, FERM head+rod with VBSs	Integrin activation, actin linkage	Couples ECM stiffness to actin remodeling	[35-36]
Kindlin-2	FERM+PH domain, binds β -integrin tail	Supports integrin clustering	Essential for adhesion, force transmission	[37]
Paxillin	68 ku, LD motifs+LIM domains	Scaffold for FAK/Src & actin linkage	Coordinates mechanical & chemical signaling	[38]
Piezo1	Trimeric ion channel, ~300 ku subunit	Ca ²⁺ influx upon stretch	Modulates chondrocyte & synoviocyte responses	[26]
YAP/TAZ	65–70 ku, Hippo effectors, transcription co-activators	Nuclear mechanotransducers	Drive fibrosis, proliferation, cartilage remodeling	[27]
HE4	~25 ku glycoprotein, WAP domains	Protease inhibition, pro-fibrotic	Elevated in RA, particularly in RA-associated fibrotic manifestations (<i>e.g.</i> , RA-ILD); links chronic inflammation to fibrosis	[29, 39]
IL-36	IL-1 family cytokine, ~160–180 aa precursors	Activates NF- κ B/MAPK, pro-inflammatory	Amplifies synovitis, promotes MMPs, and cytokine release	[30, 40]

ECM: extracellular matrix; ku: kilodalton; Ig-like: immunoglobulin-like; FERM: band 4.1/ezrin/radixin/moesin; VBS: vinculin-binding site (s); PH: pleckstrin homology; LD motifs: leucine-aspartate motifs; LIM domains: Lin-11/Isl-1/Mec-3 domains; FAK: focal adhesion kinase; Src: Src family kinase; Ca²⁺: calcium ion; NF- κ B: nuclear factor kappa-B; MAPK: mitogen-activated protein kinase; MMP: matrix metalloproteinase; WAP: whey acidic protein; aa: amino acids; RA: rheumatoid arthritis; OA: osteoarthritis; RA-ILD: rheumatoid arthritis-associated interstitial lung disease; IL: interleukin.

accompanying shift toward oxidative and inflammatory stress can perturb these regulatory checkpoints, lowering the threshold for maladaptive mechano-immune activation^[22, 41].

Across focal adhesions and the actin cytoskeleton, PTMs function as rapid “molecular switches” that control assembly-disassembly kinetics and force transmission. Rather than acting as isolated biochemical events, phosphorylation-driven turnover, force-dependent conformational switching, and regulated proteolysis collectively determine whether adhesion complexes (*e.g.*, paxillin-talin-vinculin) and actin crosslinkers (*e.g.*, filamin-A) maintain adaptive plasticity or transition toward invasive, pathogenic remodeling. When dysregulated, these PTM-dependent processes promote aberrant cytoskeletal reorganization, facilitating synovial fibroblast migration/invasion and accelerating cartilage matrix breakdown^[42-43].

Mechanotransductive hubs are similarly constrained by tightly regulated turnover. PTM-dependent control of Piezo1 responsiveness and YAP/TAZ localization ordinarily limits excessive calcium-coupled signaling and transcriptional reprogramming under physiological load. However, in chronically inflamed or stiffened arthritic microenvironments—conditions frequently amplified after menopause—loss of these restraints can sustain mechanosensitive signaling, reinforcing downstream inflammatory hubs (NF- κ B/MAPK) and pro-fibrotic/catabolic gene programs that drive tissue destruction^[22, 44].

Secreted mediators also rely on regulated maturation and stability to prevent persistent signaling. For example, enhanced stability and accumulation of HE4 can favor fibrotic ECM persistence, whereas dysregulated activation of IL-36 signaling can prolong NF- κ B/MAPK pathway engagement, amplifying chronic inflammation and matrix degradation. Thus, altered turnover of secreted effectors links inflammatory persistence to long-term structural remodeling in both OA and RA^[45-46].

Altogether, PTM- and turnover-dependent regulation determine whether joint cells remain in homeostatic adaptation or shift toward a self-sustaining pathological state. In postmenopausal arthritis, disruption of these regulatory layers—through persistent mechanosensitive signaling, aberrant cytoskeletal remodeling, and prolonged inflammatory activation—contributes directly to synovial invasion, cartilage breakdown, and fibrotic

progression.

1.3 Estrogen deficiency as a modulator of the mechano-immune axis

Estrogen plays a critical regulatory role in maintaining joint homeostasis by modulating cytoskeletal organization, mechanotransduction, and inflammatory signaling. In articular cartilage and synovium, estrogen receptor signaling (ER α , ER β , and GPER) restrains excessive mechanosensitivity and suppresses pro-inflammatory transcriptional programs. Estrogen deficiency after menopause disrupts this regulatory balance, lowering the threshold for mechano-immune activation and amplifying pathological responses to mechanical load^[47-48].

Mechanistically, this effect reflects direct estrogen receptor-dependent regulation of core mechano-immune checkpoints. At a molecular level, estrogen exerts direct regulatory control over key components of the mechano-immune axis through ER α /ER β - and GPER-mediated mechanisms. Estrogen signaling stabilizes cytoskeletal organization and focal-adhesion integrity, thereby constraining mechanosensitive calcium entry and limiting excessive Piezo1 activation under physiological mechanical load. In parallel, estrogen signaling restricts YAP/TAZ nuclear translocation by preserving Hippo pathway restraint and actin cytoskeletal tension, preventing premature activation of pro-fibrotic and catabolic transcriptional programs. Loss of estrogen removes these regulatory checkpoints, permitting exaggerated Piezo1-mediated Ca²⁺ influx, sustained YAP/TAZ nuclear localization, and heightened NF- κ B/MAPK responsiveness. Consequently, downstream inflammatory and fibrotic mediators, including IL-36 and HE4, become dysregulated, reinforcing feed-forward mechano-immune loops that amplify joint pathology in postmenopausal OA and RA^[15, 47-49].

Consistent with these receptor-mediated regulatory effects, estrogen depletion has been associated with enhanced Piezo1 responsiveness and exaggerated Ca²⁺ influx under mechanical stress, thereby promoting NF- κ B activation and chondrocyte apoptosis^[47]. In parallel, loss of estrogen signaling favors YAP/TAZ nuclear localization through altered cytoskeletal tension and focal-adhesion dynamics, shifting joint cells toward proliferative, fibrotic, and catabolic transcriptional states^[48]. These effects are further reinforced by dysregulation of adhesion and

actin-binding proteins, including vinculin, filamin-A, talin, and Kindlin-2, which become more susceptible to force-induced remodeling in estrogen-deficient tissues^[36].

Estrogen deficiency also intersects with inflammatory mediators that shape the arthritic microenvironment. Reduced estrogen signaling permits heightened IL-36 pathway activation and sustained NF- κ B/MAPK signaling, amplifying synovial inflammation, while elevated HE4 expression links chronic inflammation to fibrotic remodeling in RA. Collectively, these mechanisms position menopause as a critical biological amplifier of mechano-immune dysregulation, providing a molecular rationale for the increased incidence, severity, and heterogeneity of OA and RA in postmenopausal women^[29, 50].

An important, yet often underappreciated, distinction in postmenopausal arthritis relates to the mode of estrogen decline. Natural menopause is characterized by a gradual reduction in estrogen levels over several years, allowing partial cellular adaptation of cytoskeletal organization, mechanosensor responsiveness, and inflammatory thresholds. In contrast, surgical menopause induces abrupt and profound estrogen deprivation, which may precipitate acute mechano-immune dysregulation within joint tissues^[16].

From a mechanobiological perspective, sudden estrogen withdrawal is expected to lower the activation threshold of mechanosensitive pathways such as Piezo1, leading to exaggerated Ca^{2+} influx in response to physiological mechanical loads. This acute sensitization may, in turn, accelerate NF- κ B activation and promote early chondrocyte apoptosis. Similarly, rapid loss of estrogen-mediated cytoskeletal restraint may favor prompt nuclear localization of YAP/TAZ, shifting joint cells toward pro-fibrotic, proliferative, and catabolic transcriptional programs before compensatory mechanisms can develop^[26, 47].

In parallel, estrogen deprivation has been linked to enhanced inflammatory and fibrotic signaling. Surgical menopause may therefore be associated with a more pronounced upregulation of mediators such as HE4, which connects inflammation to tissue fibrosis, particularly in RA. By contrast, the slower hormonal transition in natural menopause may permit a more gradual evolution of mechano-immune imbalance, potentially contributing to heterogeneity in disease onset, severity, and progression among

postmenopausal women^[29].

Although direct comparative studies examining mechanotransductive markers in natural versus surgical menopause remain limited, this conceptual distinction provides a biologically plausible framework for understanding inter-individual variability in postmenopausal OA and RA. Future longitudinal and mechanistic studies are warranted to determine whether the tempo of estrogen loss differentially modulates Piezo1 activity, YAP/TAZ signaling, and HE4 expression, thereby influencing disease trajectories and therapeutic responsiveness.

1.4 Functional classification

A variety of cytoskeletal, mechanosensory, and inflammatory proteins have been identified in postmenopausal arthritis. These molecules can be grouped into functional categories based on their structural domains and biological roles. Unlike collagens, which are classified by chain composition and fibrillar organization, these biomarkers are defined by their contribution to focal adhesion integrity, actin remodeling, force sensing, and inflammatory signaling^[51]. Together, they form an interconnected network that governs cell-matrix interactions and tissue remodeling (Figure 1).

Adhesion proteins, including vinculin, talin, Kindlin-2, and paxillin, constitute the structural and signaling backbone of focal adhesions. Talin binds and activates integrins, vinculin reinforces the integrin-talin-actin linkage under force, Kindlin-2 cooperates with talin to stabilize high-affinity integrin states, and paxillin functions as a scaffold for kinases such as FAK and Src, integrating adhesion signaling with cytoskeletal dynamics. Collectively, they secure robust attachment to the ECM while enabling force transmission into biochemical pathways^[52-53].

Actin crosslinkers such as filamin-A organize actin filaments into flexible networks, providing resilience against shear stress. Its Ig-like repeat domains undergo force-dependent unfolding, exposing integrin-binding sites, allowing actin remodeling and signal propagation. Dysregulated Filamin-A dynamics alter chondrocyte and synoviocyte stiffness, a feature implicated in the mechanopathology of OA and RA^[54].

Mechanosensors, notably Piezo1 and YAP/TAZ, serve as primary force detectors. Piezo1 is a trimeric mechanosensitive ion channel that translates membrane deformation into calcium influx and downstream signaling, affecting processes such as

chondrocyte survival and inflammatory activation. YAP/TAZ are transcriptional co-activators regulated by the Hippo pathway and cytoskeletal tension; when localized in the nucleus, they drive gene programs promoting proliferation, fibrosis, and abnormal ECM deposition. Both act as central sensors linking mechanical stress to transcriptional and metabolic reprogramming^[55-56].

Inflammatory and secretory mediators further complement this classification. HE4 is a secreted

glycoprotein with protease-inhibitory activity that prevents collagen degradation, promoting fibrosis in chronically inflamed joints. IL-36 cytokines, once proteolytically activated, amplify NF- κ B and MAPK pathways in synovial fibroblasts and chondrocytes, sustaining inflammation and ECM catabolism. These secretory factors act in concert with adhesion and mechanosensory proteins to perpetuate tissue damage in postmenopausal arthritis^[30, 45].

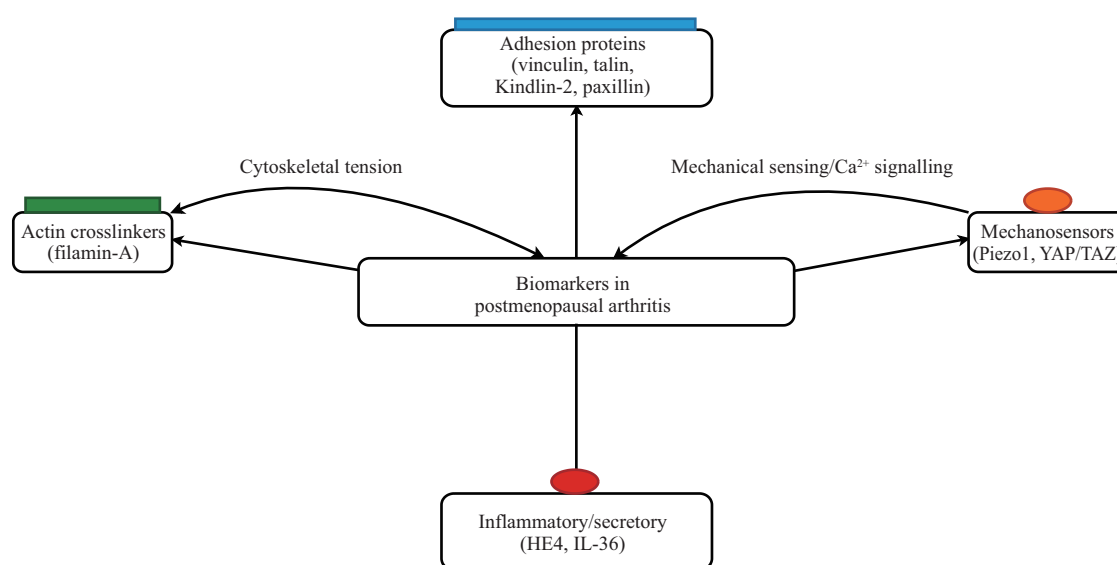


Fig. 1 Functional classification and interaction framework of emerging biomarkers in postmenopausal osteoarthritis and rheumatoid arthritis

Biomarkers are grouped into four functional classes: adhesion proteins (vinculin, talin, Kindlin-2, paxillin), actin crosslinkers (filamin-A), mechanosensors (Piezo1, YAP/TAZ), and inflammatory/secretory mediators (HE4, IL-36). Directional arrows indicate key functional interactions between these classes. Actin crosslinkers contribute to cytoskeletal tension, which influences the integrated biomarker network, whereas mechanosensors transduce mechanical sensing and Ca^{2+} -dependent signaling into downstream cellular responses. Together, this scheme highlights how structural and signaling biomarker classes are functionally interconnected at early stages of postmenopausal joint pathology, without implying detailed intracellular signaling pathways.

1.5 Expression patterns in articular cartilage and synovium

OA and RA exhibit distinct expression profiles of key mechanotransductive and inflammatory biomarkers in articular cartilage and synovium. These molecular differences explain the divergent pathological features of OA—characterized mainly by degenerative cartilage-matrix loss with mild inflammation—versus RA, which is dominated by

immune-driven synovitis and invasive pannus formation that destroys cartilage and bone^[57-58]. Table 2 provides a comparative overview of focal adhesion proteins, mechanosensors, and secreted inflammatory mediators, highlighting their expression patterns in cartilage and synovium and their roles in matrix degradation, inflammation, and bone remodeling.

Table 2 Comparative expression of cytoskeletal, mechanosensory, and inflammatory biomarkers in articular cartilage and synovium of postmenopausal osteoarthritis (OA) and rheumatoid arthritis (RA)

Biomarker	Functional group	Expression in OA (cartilage/synovium)	Expression in RA (cartilage/synovium)	Pathological role	Reference
Vinculin	Focal adhesion (integrin-actin linker)	Present in chondrocytes and synovial cells; focal adhesion distribution is altered by mechanical softening or inflammation (IL-1 β causes vinculin disassembly in chondrocytes)	Highly expressed in RA FLS focal adhesions (integrin complexes); maintains synovial cell-matrix adhesion. Not specifically upregulated in RA cartilage	Mediates mechanotransduction and cell adhesion. In OA, loss/disorganization of vinculin impairs chondrocyte attachment and promotes dedifferentiation. In RA, abundant vinculin enables FLS anchorage and invasive migration on cartilage surfaces	[33, 59-60]
Talin-1	Focal adhesion (integrin activator)	Expressed in chondrocytes; no notable OA-specific up/down-regulation reported. OA synovium shows baseline talin in resident cells	Strongly expressed in RA synovium and cultured FLS (full-length and cleaved forms detected). Enriched at RA FLS focal adhesions, co-localized with integrins	Couples integrin β cytoplasmic tails to the cytoskeleton to trigger integrin activation. In RA, high talin-1 promotes robust integrin signaling, enhancing FLS adhesion, migration, and cartilage invasion	[22, 37, 61]
Kindlin-2	Focal adhesion (integrin co-activator)	High in healthy articular chondrocytes; downregulated in OA cartilage. OA synovium: baseline low expression	Present in RA synovium (Kindlin-2 detectable in RA FLS and tissue)	Augments integrin signaling. OA: loss of Kindlin-2 impairs mechanotransduction and induces catabolic pathways. RA: Kindlin-2 in FLS supports aggressive integrin-mediated anchoring	[62-64]
Paxillin	Focal adhesion (scaffold/adaptor)	Present in chondrocytes and synoviocytes. Low activation in OA synovium (~37% of OA lining cells show active paxillin)	Highly activated in RA synovium (~77% of RA lining cells positive for active paxillin)	Coordinates the assembly of FAK-Src signaling complexes. In RA, hyperactive paxillin drives FLS invasion and monocyte recruitment. In OA, its role is secondary to matrix damage	[65-67]
Filamin-A	Cytoskeletal crosslinker (actin-binding)	Expressed in cartilage and synovium. No OA-specific change; involved in chondrogenesis	Overexpressed in RA synovium; identified as a novel autoantigen in ~56% of RA patients	Crosslinks F-actin and connects the cytoskeleton to integrins. OA: supportive role in chondrocytes. RA: dual role—structural (FLS invasiveness) and immunologic (autoantigen)	[59, 68-69]
Piezo1	Mechanosensitive ion channel	Constitutively expressed in chondrocytes. Upregulated in OA cartilage, leading to apoptosis and catabolic enzyme expression	Expressed in RA joint cells. In RA cartilage, inflammation sensitizes Piezo1; in RA FLS, Piezo1 mediates apoptosis	Converts mechanical signals to biochemical responses. OA: promotes cartilage degeneration. RA: context-dependent—aggravates cartilage injury but may limit FLS hyperplasia	[70-71]
YAP/TAZ	Mechanotransduction regulators (Hippo pathway)	Low baseline activity in cartilage. In OA, aberrantly activated, driving MMPs and suppressing collagen II and Sox9	Highly upregulated in RA synovium; abundant nuclear YAP/TAZ in RA FLS drives invasiveness, angiogenesis, and cytokine production	OA: drives cartilage catabolism. RA: endow synovium with tumour-like properties	[22, 49]

Continued to Table 2

Biomarker	Functional group	Expression in OA (cartilage/synovium)	Expression in RA (cartilage/synovium)	Pathological role	Reference
HE4 (WFDC2)	Secreted protease inhibitor (innate immunity)	Minimally expressed in OA joints; no major role	Significantly elevated in RA serum and synovium; associated with disease activity and fibrosis	OA: little role. RA: promotes fibrosis and inflammation; emerging biomarker of disease severity	[29, 72]
IL-36 ($\alpha/\beta/\gamma$)	Pro-inflammatory cytokine (IL-1 family)	Low in OA synovium; pathway is mostly inactive. Experimental activation worsens OA	Robustly upregulated in RA synovium; produced by plasma cells and activates FLS	Acts as an immune amplifier. OA: minor role unless experimentally activated. RA: key link between autoimmunity and synovial inflammation	[73-74]

IL-1 β : interleukin-1 beta; FLS: fibroblast-like synoviocytes; RA: rheumatoid arthritis; OA: osteoarthritis; FAK-Src: focal adhesion kinase/Src family kinase signaling axis; F-actin: filamentous actin; MMPs: matrix metalloproteinases; Sox9: SRY-box transcription factor 9; YAP/TAZ: Yes-associated protein/transcriptional co-activator with PDZ-binding motif.

1.5.1 Adhesion and focal adhesion proteins in OA vs RA

Vinculin, talin, Kindlin-2, and paxillin constitute the focal adhesion complex, linking integrins to the actin cytoskeleton and orchestrating mechanotransduction. In healthy cartilage, they stabilize chondrocyte morphology and confer resistance to mechanical loading. In OA, focal adhesion signaling is disrupted: Kindlin-2, normally abundant in articular chondrocytes, becomes markedly downregulated, destabilizing mechanotransduction and activating oxidative stress-driven catabolic pathways (Stat3-Runx2) that upregulate matrix-degrading enzymes. Vinculin and talin also display altered distribution under inflammatory and mechanical stress, while IL-1 β exposure can disassemble vinculin-rich adhesions, leading to impaired mechanosignaling, chondrocyte dedifferentiation, and apoptosis^[62, 75].

By contrast, RA is characterized by hyperactivation of integrin-focal adhesion signaling in synovial fibroblast-like synoviocytes (FLS). Talin-1 and Kindlin-2 are strongly co-expressed in FLS adhesions, and phosphorylated paxillin levels are more than doubled compared to OA (77% vs 37% of lining cells). This robust paxillin/FAK/Src cascade enhances FLS motility and invasiveness, driving pannus formation and direct invasion into cartilage and bone. In parallel, integrin signaling also amplifies osteoclast genesis through $\alpha\beta$ 3-FAK-Src-paxillin activation, thereby accelerating periarticular bone erosion^[52, 76].

Filamin-A, an actin crosslinker essential for cytoskeletal stability, further highlights the divergence between OA and RA. In OA cartilage, it supports mechanotransduction and has been explored as a

potential chondrogenic regulator^[77]. In RA, however, Filamin-A is highly expressed in synovial tissue but paradoxically acts as a neo-autoantigen, eliciting T- and B-cell responses that perpetuate synovitis. Thus, while focal adhesion proteins in OA reflect impaired homeostasis, in RA they become pathogenic drivers of tissue invasion, cartilage destruction, and bone remodeling^[78].

1.5.2 Mechanosensors and downstream signaling (Piezo1 and YAP/TAZ)

Piezo1, a mechanosensitive ion channel, plays a pivotal role in translating physical stress into biochemical responses. In OA chondrocytes, aberrant activation of Piezo1 by abnormal loading or fluid shear induces excessive Ca²⁺ influx, upregulates matrix-degrading enzymes (MMP-13, ADAMTS-5), and triggers apoptosis, thereby accelerating cartilage degeneration. Experimental models confirm that pharmacological inhibition of Piezo1 can attenuate these catabolic processes^[79]. In RA cartilage, pro-inflammatory cytokines such as IL-1 β sensitise Piezo1, amplifying Ca²⁺-driven injury and linking immune-mediated inflammation to mechanobiological stress. Interestingly, in RA synovium, Piezo1 activation has paradoxical effects: in FLS, mechanical stretch can trigger MAPK/ERK5-mediated apoptosis, potentially limiting hyperplasia. However, dysregulated Piezo signaling in synoviocytes and macrophages may also amplify inflammatory cascades, underscoring its dual role in RA pathogenesis^[80-81].

These divergent outcomes highlight the context-dependent nature of Piezo1 signaling across arthritic tissues. Although Piezo1 functions as a conserved mechanosensor, its downstream biological consequences are dictated by cellular identity,

inflammatory priming, and biomechanical microenvironment. In OA, Piezo1 activation in chondrocytes occurs predominantly under chronic mechanical overload within a relatively low-grade inflammatory milieu, where sustained Ca^{2+} influx promotes endoplasmic reticulum stress, mitochondrial dysfunction, and NF- κ B-driven catabolic transcriptional programs culminating in chondrocyte apoptosis and extracellular matrix degradation^[82]. In contrast, within the RA synovium, Piezo1 signaling operates in a profoundly inflammatory and hypercellular environment. Fibroblast-like synoviocytes preconditioned by high levels of TNF- α and IL-1 β exhibit altered downstream coupling, allowing Piezo1 activation to engage MAPK/ERK5-dependent apoptotic pathways that may limit hyperplasia rather than directly drive cartilage destruction^[83]. Collectively, these observations reconcile the apparent paradox of Piezo1-mediated apoptosis in RA synovium versus cartilage degeneration in OA and establish Piezo1 as a context-sensitive mechanotransducer rather than a uniformly pathogenic driver.

YAP/TAZ, nuclear effectors of the Hippo pathway, serve as master regulators of mechanotransduction and gene expression. In OA cartilage, inflammatory and mechanical cues (e.g., IL-1 β , TNF- α , excessive stiffness) aberrantly activate YAP/TAZ, driving catabolic remodeling. Nuclear YAP upregulates MMP-3, MMP-9, MMP-13, and ADAMTS-5 while repressing anabolic genes such as COL2A1 and SOX9, shifting chondrocytes toward dedifferentiation, apoptosis, and impaired repair^[49]. In RA synovium, YAP/TAZ are abundantly localized in FLS nuclei, correlating with disease severity. They promote invasiveness, cytokine release (IL-6, IL-8), and angiogenesis through downstream mediators such as Snail and Ezrin-PI3K/Akt signaling. Inhibition of YAP/TAZ in experimental RA models reduces FLS proliferation, invasiveness, and angiogenesis, highlighting them as therapeutic targets. Collectively, Piezo1 and YAP/TAZ exemplify how abnormal mechanosensing integrates with inflammation to exacerbate both cartilage degeneration in OA and synovial aggression in RA^[21, 49].

1.5.3 Secreted inflammatory mediators (HE4 and IL-36)

HE4, a secreted glycoprotein with protease inhibitor activity, remains largely quiescent in OA but is markedly elevated in RA, where it correlates with joint destruction and RA-associated interstitial lung disease^[84]. Produced predominantly by activated fibroblasts and infiltrating immune cells in inflamed

synovium, HE4 contributes to chronic inflammation and tissue remodeling by altering protease activity and extracellular matrix turnover, thereby serving as a potential biomarker for disease severity and risk stratification^[45]. Beyond its established association with fibrosis, emerging evidence positions HE4 as a mechanotransduction-responsive downstream effector within the mechano-immune axis rather than a primary mechanosensor^[85]. Current data suggest that HE4 expression is indirectly regulated by mechanical cues through canonical mechanotransductive pathways. Mechanical stress-induced activation of Piezo1-mediated Ca^{2+} influx and YAP/TAZ nuclear signaling enhances NF- κ B and MAPK activity—transcriptional programs that have been implicated in HE4 upregulation in inflammatory and fibrotic contexts^[86-87]. Within this framework, HE4 functions as an amplifier and stabilizer of chronic inflammatory and fibrotic responses by sustaining NF- κ B persistence, promoting extracellular matrix remodeling, and reinforcing fibroblast-like synoviocyte activation^[85]. Consequently, HE4 contributes to a feed-forward mechano-immune-fibrotic loop that links mechanical stress to irreversible structural joint damage, particularly in RA. IL-36, in contrast, is minimally expressed in OA under normal conditions. However, experimental models have shown that intra-articular IL-36 α accelerates OA progression if present, underscoring its potential to exacerbate cartilage loss during inflammatory flares^[88]. In RA, however, IL-36 α is strongly upregulated, particularly in CD138⁺ plasma cells within the synovium. It drives an amplification loop wherein stimulation of fibroblast-like synoviocytes induces IL-6 and IL-8 release, fueling Th17 activation and neutrophil recruitment^[50]. Collectively, HE4 and IL-36 exemplify secreted mediators that are relatively silent in degenerative OA but pathologically activated in autoimmune RA, amplifying synovial inflammation, cartilage destruction, and systemic complications^[30].

2 Pathogenic mechanisms of cartilage damage in OA and RA

Building on the above mechano-immune framework, the following section details the distinct downstream mechanisms that drive cartilage and joint damage in OA and RA.

2.1 Extracellular matrix (ECM) breakdown in osteoarthritis (OA)

ECM degradation represents a pivotal pathological hallmark of OA, resulting from the

convergence of mechanical stress and inflammatory mediators that progressively compromise cartilage integrity^[89].

Matrix-degrading enzymes (MMP-13 and ADAMTS-5): in OA, MMP-13 (collagenase-3) is the dominant enzyme responsible for cleaving type II collagen, while ADAMTS-5 (aggrecanase-2) is the principal protease degrading aggrecan. Their overexpression leads to fragmentation of cartilage structural components, weakening compressive resilience. The accumulation of these degradation products not only disrupts the extracellular matrix but also amplifies inflammatory signaling, accelerating structural breakdown^[89-90].

Filamin-A dysregulation and Piezo1 overactivation: Filamin-A normally stabilizes actin architecture and focal-adhesion integrity, thereby supporting chondrocyte resilience under mechanical load. In OA, Filamin-A dysregulation compromises cytoskeletal stability and increases vulnerability to load-induced injury. In line with upstream

mechanotransductive mechanisms, aberrant Piezo1 activation under pathological strain drives Ca^{2+} -coupled catabolic programs that promote chondrocyte apoptosis and accelerate extracellular matrix breakdown^[82, 91].

The contribution of HE4 and IL-36 to low-grade inflammation is significant, as OA is characterized by chronic, low-grade inflammation. IL-36 α , typically minimally expressed, can accelerate disease progression when upregulated, while its blockade with IL-36Ra attenuates synovitis and cartilage loss^[92]. Similarly, HE4 (WFDC2), a secreted glycoprotein, has been shown to enhance NF- κ B activity and stimulate IL-6 release, reinforcing persistent inflammatory signaling^[93]. Collectively, IL-36 and HE4 contribute to a self-perpetuating inflammatory microenvironment that exacerbates cartilage degeneration. These interrelated mechanical and inflammatory mechanisms, culminating in progressive ECM degradation and cartilage loss in OA, are summarized schematically in Figure 2.

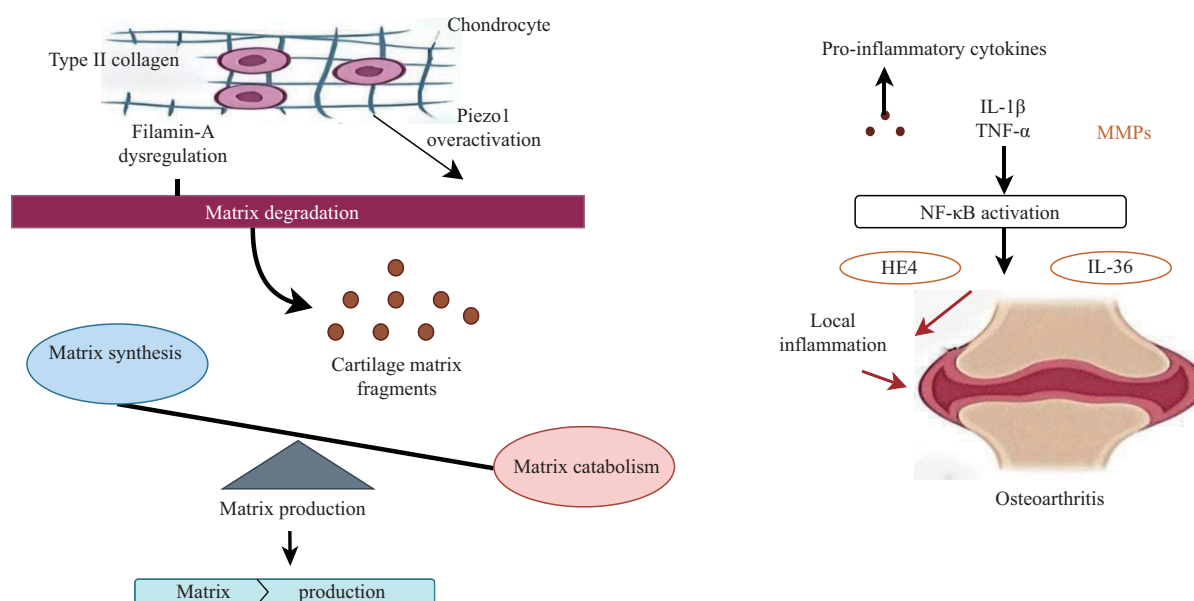


Fig. 2 Schematic representation of extracellular matrix breakdown in osteoarthritis (OA)

Converging mechanical cues (Filamin-A dysregulation, Piezo1 overactivation) together with inflammatory mediators (IL-1 β , TNF- α , HE4, IL-36) promote NF- κ B activation and MMP-driven matrix catabolism, thereby disrupting the balance between matrix synthesis and catabolism. This imbalance accelerates cartilage matrix degradation with subsequent release of cartilage matrix fragments, ultimately amplifying local inflammation and progressive cartilage damage in osteoarthritis.

2.2 Immune-mediated synovitis and cartilage invasion in RA

While Piezo1-YAP/TAZ signaling constitutes a central mechanotransductive axis, its relevance in RA becomes most evident through the downstream

inflammatory, invasive, and tissue-destructive programs it sustains.

RA is fundamentally characterized by synovial hyperplasia and the transformation of FLS into invasive, tumour-like cells that form the destructive

pannus^[14]. Molecular drivers such as talin, Kindlin-2, paxillin, and YAP/TAZ reinforce focal-adhesion signaling and cytoskeletal remodeling, thereby sustaining the migratory, invasive, and pro-inflammatory phenotype of RA FLS^[38]. Vinculin, while classically recognised as a stabilizer of talin-integrin linkages, exhibits altered localization under inflammatory stress in RA, thereby reinforcing adhesion dynamics and contributing to the invasive behavior of synoviocytes. These activated synoviocytes penetrate the cartilage surface, producing matrix-degrading enzymes and perpetuating chronic inflammation^[94].

Cytokine networks play a central role in fueling synovial invasion. Pro-inflammatory mediators, including IL-1 β and TNF- α , activate catabolic and proliferative programs in FLS, while IL-36 contributes to a feed-forward inflammatory loop, amplifying IL-6 and IL-8 release and accelerating pannus formation^[95]. In parallel, HE4 (WFDC2) has emerged as a novel inflammatory and fibrotic biomarker, not only associated with RA severity but

also linked to extra-articular manifestations such as RA-associated interstitial lung disease (RA-ILD)^[96].

Bone erosion is driven by osteoclastogenesis, orchestrated by cross-talk between integrins (*e. g.*, $\alpha\beta3$) and the RANKL/FAK/Src axis, which promotes osteoclast activation and resorptive activity at the bone-pannus interface^[97]. In addition, Filamin-A, a cytoskeletal protein, has been implicated as an autoantigen in RA, further reinforcing immune activation and joint destruction^[98].

At the cartilage-pannus interface, co-activation of β -integrins by talin-1 and Kindlin-2, together with paxillin scaffolding of FAK-Src complexes, confers tumour-like anchorage and directional invasion to RA FLS, thereby coupling adhesive mechanics to inflammatory matrix destruction^[22]. Collectively, these mechanisms converge to establish the hallmark pathological process of RA: immune-mediated synovitis evolving into invasive pannus that progressively erodes both cartilage and bone (Figure 3).

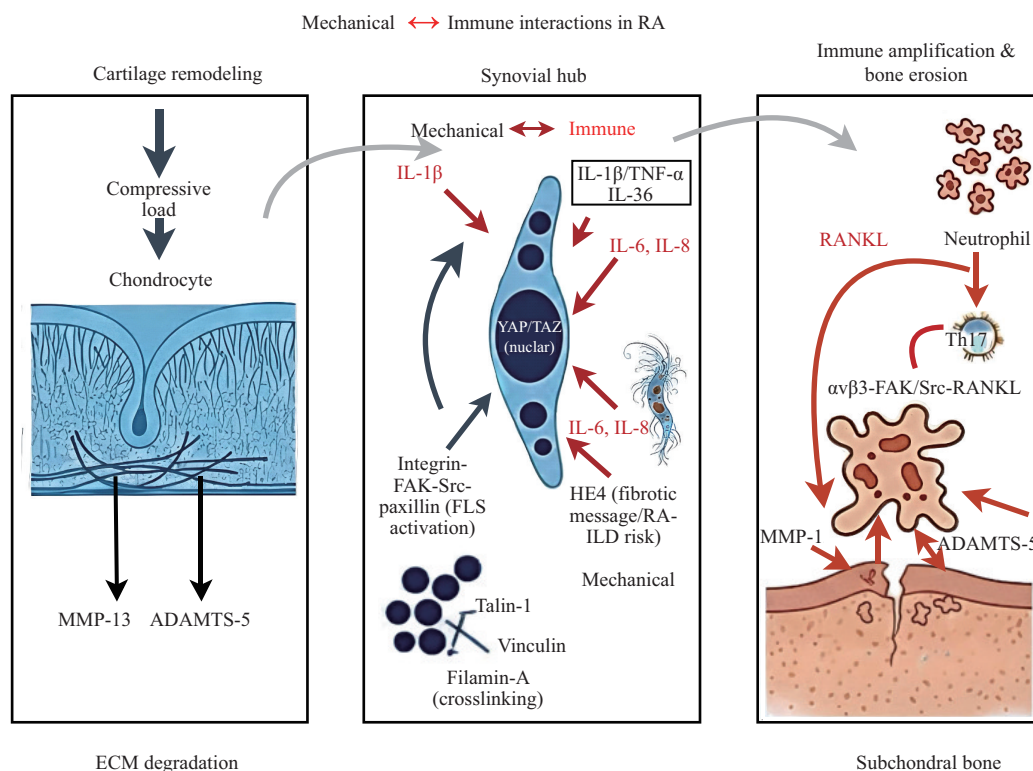


Fig. 3 Immune-mediated synovitis and pannus invasion in rheumatoid arthritis

Hyperactivated fibroblast-like synoviocytes (FLS) integrate integrin-FAK-Src-paxillin signaling with YAP/TAZ nuclear activity to drive invasion at the cartilage-pannus interface. Upstream cytokines (IL-1 β , TNF- α , and IL-36) amplify IL-6/IL-8 release, recruiting Th17 cells and neutrophils. Concurrently, HE4 sustains fibrotic remodeling and indicates RA-ILD risk. Osteoclastogenesis ($\alpha\beta3$ -FAK/Src-RANKL) mediates bone erosion. The diagram depicts cell-matrix adhesion complexes (talin-1, vinculin, filamin-A crosslinking), with downstream matrix degradation by MMP-13 and ADAMTS-5.

3 Crosstalk between mechanical stress and inflammation

This section synthesizes the bidirectional crosstalk between mechanical stress and inflammatory signaling that sustains joint pathology in OA and RA. It illustrates how mechanical cues—mediated by Piezo1 activation, focal-adhesion signaling (talin, Kindlin-2, paxillin), cytoskeletal instability (filamin-A, vinculin), and YAP/TAZ nuclear translocation—directly amplify inflammatory cascades. Conversely, pro-inflammatory cytokines and niche mediators (IL-1 β , TNF- α , IL-36, and HE4) reciprocally heighten mechanosensitivity, reinforcing Ca²⁺ influx, NF- κ B/MAPK activation, and catabolic gene programs. By contrasting OA as predominantly mechanically driven with secondary inflammation and RA as immune-driven with secondary biomechanical distortion, this section defines a feed-forward mechano-immune loop that converges on shared execution hubs to drive matrix degradation and cell death in postmenopausal joints.

3.1 Mechanical drivers amplifying inflammation

Mechanical overload initiates a mechanotransductive cascade that sensitises inflammatory signaling and lowers the activation threshold of canonical inflammatory hubs, particularly NF- κ B and MAPK. In this context, Piezo1-mediated Ca²⁺ influx functions as an established upstream trigger that can directly promote IL-6/IL-8 production, consistent with observations that pharmacological Piezo1 activation (*e. g.*, Yoda1) elevates these cytokines and demonstrates that mechanical cues alone can ignite early inflammatory responses^[26].

Upstream of NF- κ B and MAPK signaling, talin-1/Kindlin-2 co-activate β -integrins while paxillin nucleates FAK-Src signaling at focal adhesions, acting as a mechanical “switch” that converts load sensing into sustained inflammatory and catabolic programmes^[35, 41]. In parallel, inflammatory cytokines (TNF- α , IL-1 β) reinforce these circuits by sustaining YAP/TAZ-dependent transcriptional programmes that promote matrix-degrading enzymes (*e. g.*, MMP-1, MMP-13) and strengthen invasive phenotypes in both chondrocytes and fibroblast-like synoviocytes^[49].

Cytoskeletal destabilisation further amplifies this response: dysregulated Filamin-A compromises actin crosslinking and focal-adhesion integrity, reducing cellular resilience to mechanical stress and, in RA, linking mechanical instability to immune recognition through its autoantigenic potential^[98]. Likewise,

abnormal redistribution of vinculin disrupts adhesion dynamics in RA synoviocytes, facilitating inflammatory cell infiltration and reinforcing the persistence of mechano-inflammatory signaling within the joint^[99].

3.2 Inflammatory cytokines modulating mechanotransduction

IL-1 β and TNF- α have been shown to increase Piezo1 responsiveness in joint cells, creating a feed-forward loop in which cytokine-primed Piezo1 channels heighten Ca²⁺ influx and perpetuate NF- κ B-driven catabolism^[81].

Members of the IL-36 family further modulate synoviocyte mechanobiology. In RA, IL-36 α enhances FLS activation and promotes IL-6/IL-8 release, while alterations in IL-36Ra/IL-38 signaling differentially regulate FLS migration and invasion^[50]. Likewise, HE4 (WFDC2) has been implicated in sustaining chronic inflammation by upregulating NF- κ B and IL-6 pathways, effectively coupling immune signaling to mechanical stress persistence in the arthritic joint^[100].

3.3 The feedback loop: OA versus RA

Taken together, both OA and RA exhibit critical crosstalk between mechanical stress and inflammatory signaling, though the initiating drivers differ. In OA, mechanical overload predominates, eliciting low-grade inflammation and gradual extracellular matrix loss^[101]. In RA, autoimmune activation establishes invasive pannus tissue that not only drives chronic inflammation but also imposes abnormal mechanical stress on cartilage and subchondral bone^[102].

This “dual-hit model” highlights disease-specific dominance: OA as a mechanically driven disorder with secondary inflammation, and RA as an immune-driven disease that secondarily distorts joint biomechanics. This mechano-inflammatory convergence is summarized in Figure 4, which maps (left) mechanical drivers—Piezo1-mediated Ca²⁺ influx, YAP/TAZ activation, and focal-adhesion instability (Filamin-A dysregulation, vinculin mislocalization)—against (right) inflammatory priming by IL-1 β /TNF- α , IL-36-induced IL-6/IL-8 loops, and HE4-driven NF- κ B persistence, funneling centrally into NF- κ B/MAPK/JAK-STAT hubs and culminating in matrix loss and apoptosis.

4 Translational and biomarker potential of mechanotransduction pathways

This section translates the mechanobiological insights discussed above into clinically actionable frameworks, focusing on diagnostic stratification,

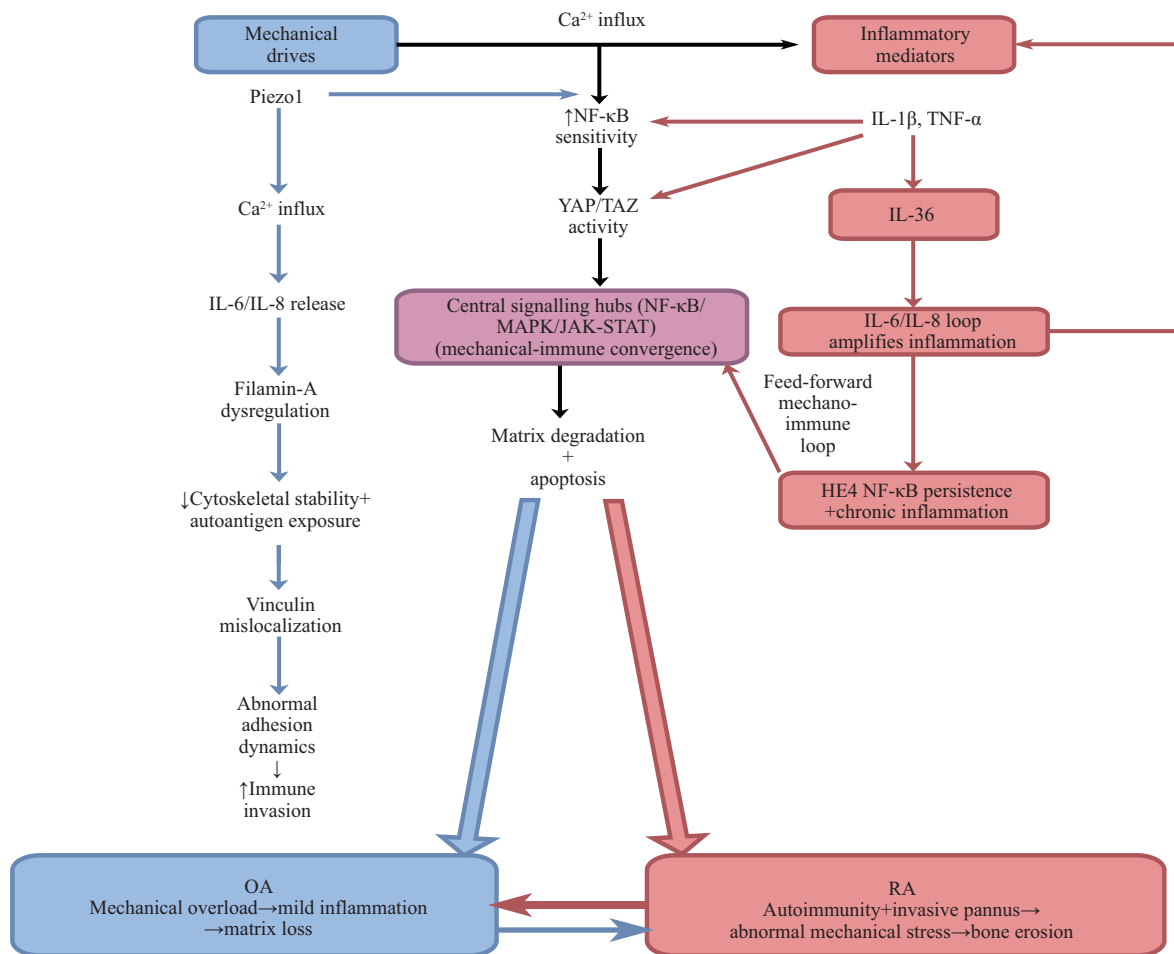


Fig. 4 Integrated mechano-immune crosstalk driving joint pathology in osteoarthritis (OA) and rheumatoid arthritis (RA)

Mechanical drivers, including abnormal joint loading, activate mechanosensitive pathways such as Piezo1-mediated Ca^{2+} influx, cytoskeletal remodeling (filamin-A dysregulation and vinculin mislocalization), and YAP/TAZ activation, thereby increasing NF- κ B sensitivity and downstream inflammatory responsiveness. In parallel, inflammatory mediators (IL-1 β , TNF- α , IL-36, and HE4) further enhance mechanosensitivity through feed-forward mechano-immune signaling loops that sustain NF- κ B, MAPK, and JAK-STAT activation. These mechanical and immune signals converge on shared intracellular signaling hubs, promoting matrix degradation, chondrocyte apoptosis, and synovial invasion. While OA is predominantly initiated by mechanical overload with secondary low-grade inflammation leading to matrix loss, RA is primarily immune-driven, characterized by invasive pannus formation, abnormal mechanical stress, and bone erosion. Together, these schematics illustrate a bidirectional mechano-immune loop that culminates in progressive joint destruction.

prognostic refinement, and emerging therapeutic opportunities. It highlights how mechanotransductive hubs—particularly Piezo1 and the YAP/TAZ axis—together with cytoskeletal adaptors and niche inflammatory mediators (HE4, IL-36/IL-38), can be integrated with conventional biomarkers to improve RA-OA discrimination, risk prediction, and patient stratification in postmenopausal women. In parallel, this section critically evaluates preclinical therapeutic strategies, precision-medicine applications, AI-assisted pathology, and regenerative approaches,

while acknowledging translational limitations and implementation challenges.

4.1 Diagnostic and prognostic applications

A multimodal panel that fuses mechanotransductive indices (Piezo1/YAP/TAZ; filamin-A/vinculin) with conventional serology (CRP, ESR, anti-CCP) yields complementary signals and reduces misclassification between OA and RA. By aligning mechanical execution pathways with immune readouts, these panels move beyond single-analyte limitations and enable phenotype-aware triage. A

multi-marker panel might integrate Piezo1/YAP/TAZ activity indices, focal-adhesion proteins (vinculin, filamin-A), and niche mediators (HE4, IL-36/IL-38) alongside classic inflammation markers (CRP, ESR, anti-CCP). For example, Filamin-A has recently been identified as an RA-specific autoantigen eliciting T/B-cell responses in over 50% of patients, whereas HE4 is elevated in RA patients with interstitial lung involvement. Such mechanobiomarkers may discriminate “mechanical” OA from “immune” RA: osteoarthritic cartilage under abnormal load tends to show high Piezo1/YAP signaling, whereas RA synovium exhibits pronounced IL-36/IL-38-mediated inflammation. Notably, conventional biomarkers alone lack full specificity: meta-analyses of RA-ILD cohorts report that CRP, ESR, and anti-CCP values overlap significantly between RA and RA-ILD. Integrating novel markers could therefore improve sensitivity and specificity in differential diagnosis and prognostication. For instance, Piezo1 channel expression/activity correlates with OA progression, and its inhibition (*e. g.*, by GsMTx4) slows cartilage degeneration. At the same time, IL-38 (an IL-36R antagonist) shows an inverse correlation with pro-inflammatory cytokines in RA and predicts disease activity^[29, 103-106].

Importantly, it should be emphasized that the current evidence supporting improved diagnostic performance of multi-marker mechano-immune panels is derived primarily from heterogeneous and exploratory studies. Consequently, reported gains in sensitivity, specificity, or overall discriminatory capacity should be interpreted as indicative trends

rather than definitive performance metrics. Rigorous prospective validation in large, well-characterized cohorts, together with assay harmonization and formal cost-effectiveness analyses, will be essential before such panels can be translated into routine clinical practice.

In addition to the need for clinical validation, several practical barriers currently limit the routine implementation of these mechano-immune panels. From a cost-effectiveness perspective, expanding diagnostic workflows beyond conventional serology (CRP, ESR, anti-CCP) to include mechanotransductive markers and cytoskeletal proteins increases assay complexity and laboratory burden. In addition, while ELISA-based quantification of circulating biomarkers (*e. g.*, HE4, IL-36, vinculin fragments) is technically feasible, functional assessment of mechanosensitivity—such as Piezo1 or YAP/TAZ activation—remains largely confined to research settings and lacks standardized clinical platforms. Pre-analytical variability, differences in tissue source (serum vs synovial fluid), and the absence of harmonized reference ranges further complicate cross-center comparability. Addressing these challenges will require assay simplification, standard operating procedures, and validation of cost-effective multiplex platforms before mechano-immune panels can transition from experimental tools to routine clinical diagnostics. As summarized in Table 3, a conceptual comparison is provided between conventional inflammatory markers and emerging mechanotransduction-related biomarkers, illustrating their relative expression

Table 3 Examples of conventional markers versus novel mechanotransduction-related biomarkers

Biomarker	OA (postmenopausal)	RA (postmenopausal)	Comment	Reference
CRP	↑ (low-grade, degenerative)	↑ ↑ (flare, high)	Acute-phase reactant	[107]
Anti-CCP	~0	High (60%–80%)	RA-specific autoantibodies	[108]
ESR	↑	↑ ↑	Nonspecific inflammation marker	[109]
Piezo1	High (mechanical stress)	Moderate (cytokine-sensitized)	Mechanosensitive ion channel	[81, 110]
YAP/TAZ	High (mechanical feedback)	Moderate (inflamed synovium)	Mechanotransduction effectors	[22]
Vinculin	Upregulated in cartilage	Upregulated in the synovium	Focal-adhesion adaptor	[99, 111]
Filamin-A	Expressed	High (autoantigenic)	RA-specific autoantigen	[98, 112]
HE4	Basal (low)	Elevated (ILD-fibrosis risk)	Fibrosis marker	[113-114]
IL-36/IL-38	Low	High	Pro-/anti-inflammatory cytokines	[30, 115]

↑ : elevated; ↑ ↑ : markedly elevated; ~0: absent/negligible. OA: osteoarthritis; RA: rheumatoid arthritis; ILD: interstitial lung disease; AUC: area under the ROC curve. Relative levels are qualitative summaries of current evidence rather than absolute concentrations; diagnostic performance of novel mechanotransductive markers (Piezo1, YAP/TAZ, vinculin, filamin-A, HE4, IL-36/IL-38) requires validation in large, independent cohorts. Notably, Filamin-A has emerged as an RA-associated autoantigen, whereas HE4 correlates with RA-ILD risk. talin-1, Kindlin-2, and paxillin are core components of the integrin-FAK adhesion axis with strong mechanistic evidence in RA/OA tissue studies; however, their clinical assay validation (serum/synovial sensitivity, specificity, AUC) is currently investigational, and thus they are listed here as exploratory adhesion markers rather than established diagnostic biomarkers.

patterns and potential diagnostic relevance in postmenopausal OA and RA.

4.2 Therapeutic targeting of mechanotransduction

Piezol inhibitors (*e. g.*, GsMTx4). Blocking Piezol-mediated Ca^{2+} influx can halt mechano-inflammatory signaling. In preclinical models, GsMTx4 markedly attenuates cartilage damage, chondrocyte apoptosis, and the release of inflammatory mediators in loaded joints. Such agents aim to “break” the early feed-forward loop of mechanical stress and IL-1 β -driven NF- κ B activation in OA^[26, 116].

YAP/TAZ inhibitors (*e. g.*, verteporfin). Pharmacological inhibition of the Hippo pathway effectors YAP/TAZ can suppress matrix catabolism. YAP/TAZ are known to drive MMP-13 and other catabolic gene expression in response to cytokine and stretch stimuli. Verteporfin (a YAP inhibitor) has been shown in animal studies to reduce aggressive rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) behavior and MMP levels, and might similarly protect cartilage from degeneration^[117-118].

HE4 blockade. Given HE4’s role in fibrotic remodeling, anti-HE4 therapies could mitigate RA-associated ILD. HE4 promotes fibrosis *via* MAPK/MMP/NF- κ B pathways; neutralizing HE4 has shown anti-fibrotic effects in lung models. In RA-ILD, HE4 levels correlate with fibrosis on imaging, so that HE4 antagonists may prevent lung complications^[45, 119].

IL-36 receptor antagonists (IL-36Ra, IL-38). Restoring the balance of IL-36 signaling can quell synovial inflammation. IL-38 (an IL-36R antagonist) is a potent anti-inflammatory cytokine whose deficiency worsens RA. Clinical data show IL-38 levels inversely track IL-6/IL-17 and disease activity, and exogenous IL-38/IL-36Ra can dampen pathogenic Th17 responses. Blocking the IL-36/IL-1 axis may therefore interrupt chronic synovitis^[30, 88].

Focal-adhesion stabilization. Strengthening cartilage focal adhesions (*e. g.*, stabilizing vinculin-actin linkages or filamin networks) could reinforce tissue integrity. For example, mimetics that enhance vinculin binding or filamin-A crosslinking might resist the FLS invasion and cartilage erosion seen in RA. While still conceptual, targeting adhesion complexes may help maintain homeostasis under stress^[120-121].

4.3 Integration into precision and regenerative medicine

Mechanotransductive biomarkers can be woven into next-generation diagnostics and therapies for arthritis.

(1) Point-of-care/liquid biopsy. Rapid assays (ELISA or biosensor-based) for HE4, filamin-A, vinculin, or IL-38 in blood or synovial fluid would enable bedside stratification. For instance, rapid assays quantifying HE4, alone or in combination with cytoskeletal markers such as Filamin-A, may help identify patients at risk of RA-associated interstitial lung disease (RA-ILD) or early systemic involvement, analogous to the clinical use of anti-CCP antibodies. Such multiplexed liquid biopsy approaches warrant further validation for point-of-care implementation^[29, 122].

(2) Omics-driven profiling. Transcriptomic, proteomic, and metabolomic data from patient samples can be combined with mechanobiology profiles. Integrating, say, cartilage RNA-seq (reflecting YAP/IL-36 pathway activation) with serum cytokines and clinical scores will help define molecular subtypes (*e. g.*, “mechanical/OA-predominant” vs “immune/RA-predominant”). Machine learning on these multi-omic datasets can reveal signatures that guide personalized therapy choices^[123-124].

(3) Mechanoresponsive biomaterials. In tissue engineering, novel scaffolds could be engineered to sense Piezol or YAP/TAZ signals. For example, a cartilage graft impregnated with Piezol-activatable gel beads might release anabolic factors in response to mechanical load, promoting adaptive regeneration. Similarly, IL-36-responsive hydrogel implants could locally modulate inflammation in arthritic joints. Designing “smart” biomaterials tuned to mechanotransductive pathways would bridge mechanical rehabilitation and molecular therapy^[125-126].

(4) Precision medicine. Ultimately, treatments can be tailored to an individual’s biomarker profile. Patients with high mechanosensor activity (*e. g.*, elevated Piezol transcripts or YAP nuclear localization) might preferentially receive mechanoregulation therapies (joint offloading, Piezol inhibitors). Those with dominant IL-36/TLR signatures may get specific cytokine inhibitors. In practice, this means using biomarker panels to decide which patients need aggressive DMARDs/biologics versus those likely to benefit from mechanical interventions or emerging mechano-targeted drugs^[127-128].

4.4 Conceptual framework (novelty anchor)

OA and RA as mechano-immune syndromes: the unifying theme is that tissue mechanics and immunity are intertwined in both diseases. Rather than viewing OA as “just wear-and-tear” and RA as “just

autoimmunity,” this framework posits that mechanical stress always feeds into inflammation, and vice versa. For example, mechanical loading of cartilage activates Piezo1 in mesenchymal/stem cells, which in turn polarizes Th17 cells and drives synovitis. Conversely, chronic inflammation (TNF/IL-1) sensitizes mechanosensors and amplifies downstream NF- κ B and YAP pathways, creating a vicious feed-forward loop^[129-130]. In other words, OA is partly immune-driven by stress, and RA is partly mechano-

driven by dysregulated load. This concept is schematized in Figure 5, a translational roadmap: mechanotransduction biomarkers lead to new diagnostic assays, enabling refined prognosis, which in turn highlight therapeutic targets, ultimately feeding into precision and regenerative medicine applications. By anchoring our strategy in this mechano-immune model, we provide a novel perspective that elevates the clinical relevance of mechanotransduction.

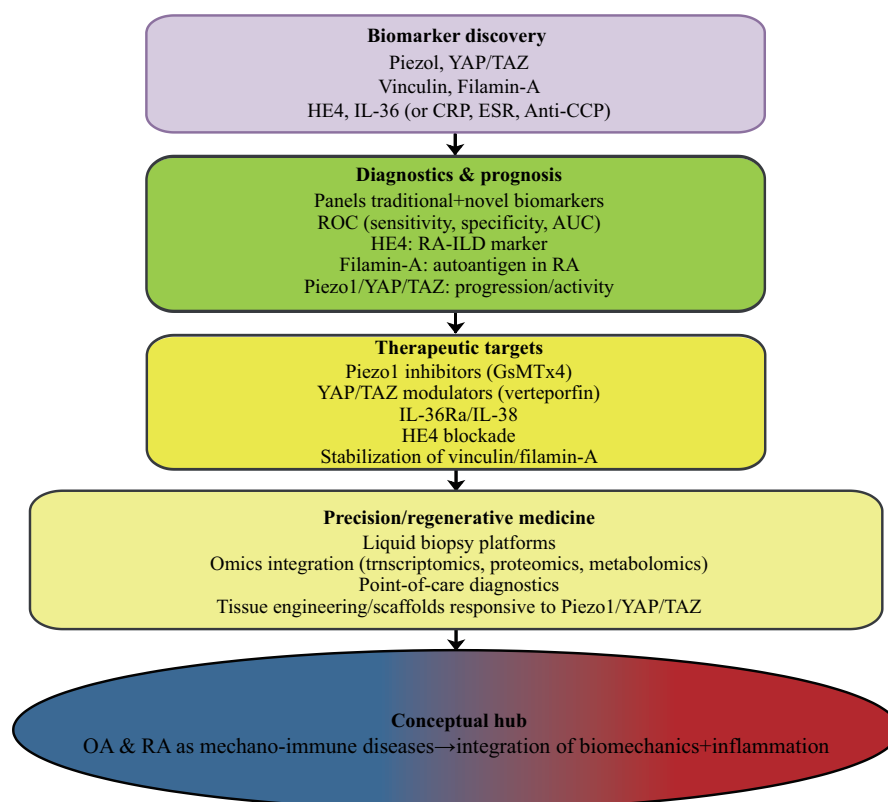


Fig. 5 Translational roadmap for mechano-immune research in osteoarthritis (OA) and rheumatoid arthritis (RA)

The diagram illustrates a bench-to-bedside translational pipeline linking mechanobiological discovery to clinical application. It summarises the progression from biomarker discovery (Piezo1, YAP/TAZ, vinculin, filamin-A, HE4, IL-36) to diagnostic and prognostic stratification through integrated biomarker panels and ROC-based performance metrics. The roadmap further highlights emerging therapeutic targets—primarily at preclinical or early translational stages—including modulation of Piezo1, YAP/TAZ, IL-36 signaling, HE4-associated fibrosis, and cytoskeletal stabilization. Finally, precision and regenerative medicine strategies are outlined, encompassing liquid biopsy platforms, multi-omics integration, point-of-care diagnostics, and mechano-responsive tissue engineering approaches. Collectively, the schematic conceptualizes OA and RA as mechano-immune disorders and provides a structured framework for translating mechanotransduction research into personalized clinical interventions.

4.5 Computational pathology and AI-enabled biomarker readouts

Recent advances in AI-driven histopathology enable slide-level inference of biomarker states directly from routine hematoxylin and eosin staining (HE staining) and immunohistochemistry (IHC) images, offering scalable, objective quantification of

mechano-immune phenotypes^[131]. Weakly supervised deep learning on whole-slide images (WSIs) can capture nuclear YAP/TAZ localization, focal-adhesion enrichment (*e. g.*, vinculin/paxillin patterns), and stromal-immune architecture, thereby inferring pathway activation that complements serological testing and multiplex immunoassays. Practically,

multimodal pipelines that fuse digital pathology with synovial/circulating biomarker panels (HE4, IL-36/IL-38, Piezo1/YAP signatures) and clinical metadata can yield robust risk scores for RA-OA discrimination, progression, and RA-associated ILD^[132]. To ensure safe adoption, models should undergo cross-site external validation, bias auditing, pre-analytical standardisation, and explainability analyses (*e. g.*, attention heatmaps, cell-level attributions), with governance for data privacy and model-drift monitoring before deployment into diagnostic workflows^[132].

4.6 Immunopathology integration

Mechanotransduction unfolds within an immune effector layer. In RA, IL-36-high synovium, Th17 skewing, neutrophil protease activity, and fibroblast-myeloid crosstalk cooperates with YAP/TAZ-centric mechanics to consolidate pannus invasiveness; in OA, low-grade cytokine tone modulates Piezo1 responsiveness under abnormal load. Accordingly, composite panels pairing mechanosensors/adhesion proteins (Piezo1, YAP/TAZ, filamin-A, vinculin) with immune readouts (IL-36/IL-38 balance, IL-6/IL-8) are poised to stratify mechano-immune phenotypes and guide therapy selection^[22, 30, 47].

5 Therapeutic options and clinical perspectives

This section translates the mechano-immune framework into actionable therapeutic and clinical perspectives, spanning pharmacological targeting, cytoskeletal stabilization, regenerative strategies, and precision medicine. It synthesises emerging interventions aimed at interrupting pathological force-inflammation feedback loops, including modulation of Piezo1, YAP/TAZ, IL-36 signaling, HE4-driven fibrosis, and focal-adhesion dynamics. Beyond experimental therapies, the section critically evaluates translational readiness, drug repurposing opportunities, and patient stratification approaches, with particular emphasis on postmenopausal women as a high-risk population. By integrating mechanobiology with clinical decision-making, this section outlines a realistic pathway from molecular

insight to personalized intervention while acknowledging current limitations and implementation challenges.

5.1 Pharmacological targeting of mechanotransduction

Therapeutic opportunities cluster around four axes: Piezo1 inhibition, YAP/TAZ modulation, IL-36/IL-38 rebalancing, and adhesion/cytoskeletal stabilisation; together, these strategies interrupt mechano-immune feed-forward loops that drive tissue destruction^[87]. Chronic joint stress drives inflammation *via* mechanosensors; blocking these signals can halt disease cascades. Piezo1 inhibitors (*e. g.*, the peptide GsMTx4) prevent stress-induced Ca^{2+} influx and downstream NF- κ B activation, breaking the early inflammatory loop. Indeed, GsMTx4 markedly reduced cartilage damage and chondrocyte death in OA models^[133]. YAP/TAZ inhibitors (*e. g.*, verteporfin) curb synoviocyte aggression by suppressing matrix metalloproteinases and pannus formation^[22]. In RA models, verteporfin reduced TNF- α -induced MMP-1 and IL-6, confined FLS invasiveness, and improved arthritis severity^[134]. IL-36 axis modulators—namely IL-36 receptor antagonists and IL-38—rebalance synovial cytokines. Exogenous IL-38 or IL-36Ra shifts macrophages and FLS towards anti-inflammatory phenotypes. Preclinical data show IL-38 overexpression in arthritic joints greatly attenuates inflammation and lowers TNF α /IL-17 production^[135]. HE4 antagonists target fibrotic RA complications. HE4 is upregulated in fibrotic lung and joint disease, driving fibroblast activation *via* annexin II. *In vivo*, knocking down HE4 markedly reduces pulmonary fibrosis, making HE4 blockade (antibody or shRNA) a novel anti-fibrotic strategy^[45].

Drug repurposing is a key theme: verteporfin (an FDA-approved angiogenesis inhibitor) and GsMTx4 (studied in cardiac mechano-physiology) exemplify how existing drugs can be redirected. For instance, verteporfin's anti-YAP activity in oncology models suggests repurposing for synovitis^[136]. Together, these approaches demonstrate that mechanobiological targets can yield translational therapies (Table 4).

Table 4 Therapeutic targets within mechanotransduction and adhesion pathways in OA and RA: mechanisms, strategies, and current development status

Target	Mechanism of action	Therapeutic strategy	Status	Reference
Piezo1	Blocks Ca^{2+} influx $\rightarrow$ NF- κ B inhibition	GsMTx4 (peptide inhibitor)	Preclinical	[137-138]
YAP/TAZ	Suppress MMPs & pannus invasion	Verteporfin (repurposed drug)	Preclinical/oncology trials	[139-140]
IL-36/IL-38	Modulate synovial inflammation	IL-36Ra; recombinant IL-38	Preclinical	[141]
HE4	Anti-fibrotic, RA-ILD prevention	HE4 antibody/shRNA	Preclinical/fibrosis models	[45]

Continued to Table 4

Target	Mechanism of action	Therapeutic strategy	Status	Reference
Filamin-A/vinculin	Stabilize focal adhesions, prevent invasion	Peptide stabilizers (experimental)	Conceptual	[64, 142]
Talin-1/Kindlin-2/paxillin	Upstream integrin-FAK activation	Exploratory adhesion modulators	Conceptual	[52, 61]

OA: osteoarthritis; RA: rheumatoid arthritis; ILD: interstitial lung disease; FLS: fibroblast-like synoviocytes; NF- κ B: nuclear factor kappa-B; MMP-13: matrix metalloproteinase-13; FAK: focal adhesion kinase. Status categories are based on currently available literature. preclinical: tested *in vitro*/*in vivo* experimental models; clinical: evaluated in patients; repurposing: drugs in use for other indications with potential arthritis applications; conceptual: mechanistic evidence without therapeutic validation. Exploratory adhesion markers (talin-1, Kindlin-2, paxillin) are included as upstream regulators of the integrin-FAK axis, but remain investigational with no established diagnostic/therapeutic assays.

5.2 Cytoskeletal and focal adhesion stabilisation

Another strategy is to stabilize cell-matrix adhesions. Proteins like filamin-A and vinculin anchor the actin cytoskeleton to integrin complexes; enhancing their function could rigidify the adhesion network and impede FLS invasion^[143]. Although still in their early stages of development, filamin-A/vinculin-targeting peptides or small molecules might reinforce the cytoskeletal scaffold and preserve cartilage integrity (Table 4). Upstream regulators in the integrin-FAK axis (talin-1, Kindlin-2, paxillin) are also of interest. These proteins initiate focal-adhesion signaling; experimental adhesion modulators could tune integrin activation to reduce motility. Such approaches are at an exploratory stage, but by fortifying cellular attachments, they could synergise with anti-inflammatory therapies to limit pannus growth^[64, 144].

5.3 Regenerative and biomaterials approaches

Regenerative medicine offers smart solutions that address mechanical processes. Mechanoresponsive scaffolds and hydrogels can be engineered to sense local forces and release therapeutics. For example, piezoelectric hydrogels generate electrical cues under load, promoting matrix deposition and stem cell differentiation. Piezoelectric nanofibrous scaffolds, under physiological strain, greatly enhance ECM production and chondrogenesis^[145]. One could envision matrices embedded with Piezo1- or YAP-sensitive elements that liberate growth factors during movement, or scaffolds incorporating IL-36/IL-38 moieties to neutralise inflammation locally^[146]. Smart implants—such as 3D-printed devices—could contain drug reservoirs that dispense anti-inflammatory or mechano-modulatory agents on demand. Finally, tissue-engineered cartilage can integrate these concepts, such as autologous cartilage grafts seeded in mechanoresponsive matrices to support repair in postmenopausal women (after menopause, declining estrogen impairs cartilage resilience; such implants could compensate by providing tailored biomechanical cues). These biomaterial strategies are

emerging and have not yet reached clinical trials, but they point toward future precision therapies^[147-148].

5.4 Clinical perspectives and personalized medicine

A precision approach tailors intervention to patient signatures. For instance, patients with high Piezo1 expression or hyperresponsive joints might benefit from joint unloading (orthotics/physiotherapy) and Piezo1 inhibitors. Patients driven by an IL-36-high profile (*e. g.*, robust synovial IL-36 γ) might receive targeted cytokine-blockade (analogous to IL-36R blockers in dermatology). Those with elevated HE4 would be monitored for RA-ILD and considered for anti-fibrotic therapy^[149-150].

Postmenopausal women require special focus. Menopause is a novel aspect of our model: hormonal decline weakens the cartilage/immune interface. Indeed, meta-analysis shows postmenopausal women have a significantly higher RA risk than premenopausal peers (odds ratio ~ 1.35)^[151]. Estrogen normally supports bone and cartilage homeostasis; its loss leads to subchondral bone resorption and cartilage thinning, compounding mechanical vulnerability. Recognising this, clinical strategies for older women could combine hormonal support with mechano-targeted drugs. In sum, personalizing therapy by biomarker profile and hormonal status could amplify efficacy^[152].

5.5 Clinical translation landscape

To date, no registered clinical trials directly target Piezo1, YAP/TAZ, HE4, or IL-36 in arthritis. However, experience from other fields points to fast-follower potential. For example, IL-36R antagonists (spesolimab, imsidolimab) have shown efficacy in pustular skin disease, earning FDA approval, which suggests they could be repurposed for synovitis^[153]. Verteporfin is being tested as a YAP inhibitor in oncology, and our preclinical work (Table 4) argues for trials in inflammatory arthritis. Notably, HE4-targeting approaches proved anti-fibrotic in pulmonary models, implying that anti-HE4 drugs could prevent RA-ILD progression^[140]. One might

summarize: no RCTs exist yet in arthritis for these targets; however, lessons from oncology and fibrosis suggest imminent translational opportunities. As new inhibitors move through clinical pipelines, early-phase trials in RA/OA—possibly *via* drug-repurposing protocols—should be prioritized. A schematic overview of this translational trajectory—from target discovery and preclinical validation to repurposing, clinical translation, and ultimately precision and regenerative applications—is schematically illustrated in Figure 6.

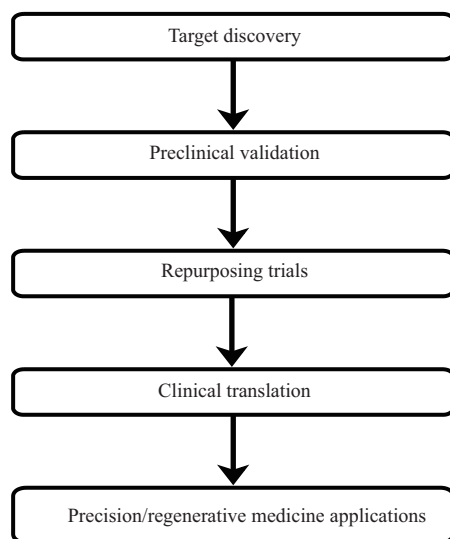


Fig. 6 Translational pipeline of mechano-immune targets in osteoarthritis and rheumatoid arthritis

The diagram summarizes the stages from target discovery and preclinical validation through drug repurposing and clinical translation to precision and regenerative medicine applications.

5.5.1 Clinical trial status and translational readiness

At present, most mechano-immune-targeted therapeutic strategies discussed in this review—including Piezo1 inhibition and YAP/TAZ blockade—remain at the preclinical stage^[8]. Based on keyword searches of major clinical trial registries (ClinicalTrials.gov (<https://clinicaltrials.gov>) and the EU Clinical Trials Register (<https://www.clinicaltrialsregister.eu>); accessed January 2026), we did not identify phase I/II interventional trials directly evaluating Piezo1-, YAP/TAZ-, HE4-, or IL-36-targeted interventions in OA or RA. Nevertheless, translational progress is emerging through adjacent clinical fields. IL-36 receptor antagonists (*e. g.*, spesolimab and imsidolimab) have demonstrated clinical efficacy and safety in inflammatory dermatologic disorders, supporting the feasibility of repurposing IL-36-axis modulation for synovial

inflammation^[153-154]. Likewise, verteporfin—an FDA-approved agent currently under clinical evaluation as a YAP inhibitor in oncology—represents a potential repurposing candidate, contingent upon joint-specific delivery and safety optimization^[155-156]. Overall, these observations indicate that although mechano-immune therapeutic concepts are not yet clinically validated in OA or RA, their mechanistic alignment with agents already in clinical pipelines supports a realistic trajectory toward early-phase translational studies, provided that proof-of-concept and phase I safety assessments are prioritized.

5.5.2 Translational challenges and considerations

While mechano-immune-targeted strategies offer compelling translational opportunities, several challenges must be addressed before clinical implementation. Effective intra-articular delivery remains a major hurdle due to rapid synovial clearance and the need for sustained, site-specific bioavailability. Moreover, key mechanotransductive regulators, including Piezo1 and YAP/TAZ, are widely expressed across multiple tissues, raising concerns regarding targeting specificity and potential systemic adverse effects. These issues are particularly relevant in chronic conditions such as OA and RA, where long-term modulation of mechanosensitive pathways may disrupt physiological tissue adaptation and repair. Collectively, these limitations underscore the necessity for advanced local delivery platforms, selective pathway modulation, and rigorous early-phase clinical evaluation to balance therapeutic efficacy with long-term safety.

5.6 Clinical risk stratification

Patient-level heterogeneity substantially modulates mechanobiomarker expression and performance. In postmenopausal women, estrogen decline accelerates subchondral bone loss and stromal fibrosis, amplifying YAP/TAZ programs; obesity increases joint loading and alters cytokine tone, sensitising Piezo1 and integrin signaling; smoking and genetic predisposition (autoantibody status) further bias synovial immunity^[157-158]. To operationalise precision care, we propose a tiered approach:

(1) Baseline signature: CRP/ESR, anti-CCP plus core mechanomarkers (Piezo1/YAP indices, filamin-A, vinculin) and niche mediators (HE4, IL-36/IL-38).

(2) Risk modifiers: menopausal status, BMI, smoking, prior flares, extra-articular disease (*e.g.*, RA-ILD risk flagged by HE4).

(3) Actionable strata: mechanical-predominant OA→offloading+Piezo1/adhesion-supportive strategies; immune-predominant RA→cytokine-axis targeting; mixed→combination therapy

with staged sequencing.

5.7 Limitations & implementation challenges

(1) Despite the promising therapeutic potential of targeting mechanotransductive regulators such as Piezo1 and YAP/TAZ, several challenges limit their immediate clinical translation. Achieving effective local drug delivery within the joint remains difficult due to rapid synovial clearance and the need for repeated intra-articular injections. In addition, Piezo1 and YAP/TAZ are widely expressed in multiple tissues, raising concerns about systemic off-target effects if inhibitors are administered chronically. Importantly, most available evidence for these therapeutic strategies is derived from preclinical models, and robust data on long-term safety, joint-specific bioavailability, and optimal dosing in humans is still lacking. These limitations highlight the need for improved local delivery systems and careful safety evaluation before clinical application.

(2) Biomarker specificity. A key limitation of the proposed mechano-immune biomarkers is their limited disease exclusivity. Molecules such as HE4, YAP/TAZ, and Filamin-A are not arthritis-specific. They may also be altered in systemic or fibrotic conditions that frequently coexist in postmenopausal women, including malignancy, cardiovascular disease, and age-related tissue remodeling. Consequently, elevations in these markers cannot be interpreted as arthritis-specific when assessed in isolation.

(3) Context-dependent pathogenic relevance. Importantly, the significance of these biomarkers in OA and RA is context-dependent, arising from joint-specific localization, pathway coupling, and coordinated activation within mechano-immune networks rather than absolute circulating levels. For example, YAP/TAZ activation in mechanically stressed chondrocytes or synovial fibroblasts reflects local mechano-inflammatory reprogramming distinct from activation observed in oncogenic or fibrotic tissues.

(4) Mitigation strategies. To mitigate specificity limitations, this review emphasizes integrated multi-marker panels combining mechanotransductive regulators, cytoskeletal proteins, inflammatory mediators, and established clinical indices (*e.g.*, DAS28 and imaging findings). Such pattern-based approaches reduce confounding from systemic comorbidities and improve disease discrimination, although prospective validation in large, well-characterized cohorts remains essential.

(5) Regulatory and standardization. Clinical deployment of mechanobiology-informed diagnostics requires assay standardization, pre-analytical standard

operating procedures (SOPs), and robust evidence of clinical validity and utility under FDA/EMA frameworks. Reference ranges for novel targets (*e.g.*, Filamin-A, HE4) must be established in multi-centre, demographically diverse cohorts with harmonized sampling and readout protocols.

(6) Inter-patient variability. Age, menopausal state, comorbidities, and genetics influence biomarker baselines and biodistribution, complicating universal cut-offs. Prospective studies should incorporate calibration by risk factors (*e.g.*, BMI, smoking) and use external validation across sites to ensure generalizability and mitigate spectrum bias.

(7) AI integration. Digital pathology and multimodal ML face risks of domain shift, bias, and limited interpretability. Mitigations include cross-site external validation, model cards/datasheets, drift monitoring, and clinician-in-the-loop review with explainable outputs (*e.g.*, slide-level attention maps and cell-level attributions) before clinical deployment.

6 Conclusion

OA and RA should no longer be viewed as merely degenerative or autoimmune diseases but as mechano-immune disorders in which mechanical stress and inflammatory signaling are inseparably interconnected. By integrating conventional inflammatory biomarkers (CRP, ESR, anti-CCP) with emerging mechanotransductive and cytoskeletal mediators—including Piezo1, YAP/TAZ, vinculin, filamin-A, HE4, and IL-36/IL-38—our review highlights the potential of multi-marker diagnostic panels to achieve more precise disease differentiation and prognostication, particularly in postmenopausal women. In parallel, the integrin-FAK adhesion axis—anchored by talin-1, Kindlin-2, and paxillin—links tissue load to inflammatory execution programs, underscoring its promise as an exploratory biomarker and an upstream therapeutic entry point within the mechano-immune framework. Importantly, translational perspectives now extend beyond biomarker discovery toward targeted interventions: Piezo1 inhibition, YAP/TAZ blockade, HE4 antagonism, IL-36 modulation, and stabilization of cytoskeletal/focal adhesion proteins represent promising pharmacological and regenerative strategies. The development of mechanoresponsive scaffolds, smart biomaterials, and precision-medicine frameworks tailored to postmenopausal women further strengthens the therapeutic potential of this paradigm. Nevertheless, current evidence remains limited by the scarcity of large, multi-centre clinical

cohorts and the predominance of preclinical data, underscoring the urgent need for rigorous validation and early-phase translational trials. Forward outlook. Next-generation studies should prioritise multi-centre validation of mechanotransductive panels, AI-enabled slide analytics for mechano-immune quantification, and mechanosensitive biomaterials that couple diagnosis with therapy. By integrating multi-omics with digital pathology and risk stratification in postmenopausal women, this paradigm can accelerate trial readiness and enable personalized, disease-modifying interventions in RA and OA. Taken together, reframing OA and RA as mechano-immune syndromes provides a novel conceptual and clinical framework with the potential to transform diagnostic algorithms, prognostic tools, and therapeutic strategies, ultimately paving the way for precision and regenerative medicine in arthritis.

Acknowledgement The authors acknowledge the use of ChatGPT (OpenAI) to assist in language editing and textual refinement during the preparation of this manuscript. All scientific content, data interpretation, and conclusions were developed and validated by the authors without the use of AI tools.

References

- [1] Di X, Gao X, Peng L, *et al*. Cellular mechanotransduction in health and diseases: from molecular mechanism to therapeutic targets. *Signal Transduct Target Ther*, 2023, **8**(1): 282
- [2] Yao M, Tijore A, Cheng D, *et al*. Force- and cell state-dependent recruitment of Piezo1 drives focal adhesion dynamics and calcium entry. *Sci Adv*, 2022, **8**(45): eabo1461
- [3] Nardone G, Oliver-De La Cruz J, Vrbsky J, *et al*. YAP regulates cell mechanics by controlling focal adhesion assembly. *Nat Commun*, 2017, **8**: 15321
- [4] Sun Z, Guo S S, Fässler R. Integrin-mediated mechanotransduction. *J Cell Biol*, 2016, **215**(4): 445-456
- [5] Boutet M A, Nerviani A, Lliso-Ribera G, *et al*. Interleukin-36 family dysregulation drives joint inflammation and therapy response in psoriatic arthritis. *Rheumatology*, 2020, **59**(4): 828-838
- [6] Yan S, Peng Y, Wu Z, *et al*. Human epididymis protein 4 (HE4) is a novel biomarker for fibrosis in IgG4-related disease and can predict poor prognosis. *RMD Open*, 2022, **8**(2): e002521
- [7] Yan R, Li Y, Chen S, *et al*. Mechanotransduction in shaping immunity: pathways, crosstalk, and pathophysiological relevance. *Adv Sci*, 2025, **12**(41): e12164
- [8] Lei C, Wu D, Zhang H, *et al*. The mechanotransduction-immune axis in organ fibrosis: dual regulatory mechanisms and translational therapeutic perspectives. *Front Immunol*, 2025, **16**: 1670213
- [9] Park E H, Choi S T, Song J S, *et al*. Effects of cumulative lifetime estrogen exposure on the clinical characteristics and courses in postmenopausal women with rheumatoid arthritis. *Semin Arthritis Rheum*, 2025, **74**: 152790
- [10] Castañeda S, Vicente-Rabaneda E F. Disentangling the molecular interplays between subchondral bone and articular cartilage in estrogen deficiency-induced osteoarthritis. *Osteoarthritis Cartilage*, 2023, **31**(1): 6-8
- [11] Allen K D, Thoma L M, Golightly Y M. Epidemiology of osteoarthritis. *Osteoarthritis Cartilage*, 2022, **30**(2): 184-195
- [12] Finckh A, Gilbert B, Hodkinson B, *et al*. Global epidemiology of rheumatoid arthritis. *Nat Rev Rheumatol*, 2022, **18**(10): 591-602
- [13] Atukorala I, Hunter D J. A review of quality-of-life in elderly osteoarthritis. *Expert Rev Pharmacoecon Outcomes Res*, 2023, **23**(4): 365-381
- [14] Gao Y, Zhang Y, Liu X. Rheumatoid arthritis: pathogenesis and therapeutic advances. *MedComm*, 2024, **5**(3): e509
- [15] Atasoy-Zeybek A, Showel K K, Nagelli C V, *et al*. The intersection of aging and estrogen in osteoarthritis. *NPJ Womens Health*, 2025, **3**(1): 15
- [16] Namavari N, Joka M, Ghodsian A, *et al*. Menopausal state and rheumatoid arthritis: a systematic review and meta-analysis. *BMC Rheumatol*, 2024, **8**(1): 48
- [17] Selim A M, Elsabagh Y A, El-Sawalhi M M, *et al*. Serum lncRNA ITGB2-AS1 and ICAM-1 as novel biomarkers for rheumatoid arthritis and osteoarthritis diagnosis. *BMC Med Genomics*, 2024, **17**(1): 247
- [18] Zheng Q, Lan Y, Chen J, *et al*. Identification and validation of CKAP2 as a novel biomarker in the development and progression of rheumatoid arthritis. *Front Immunol*, 2025, **16**: 1606201
- [19] Liang J, Yi Q, Liu Y, *et al*. Recent advances of m6A methylation in skeletal system disease. *J Transl Med*, 2024, **22**(1): 153
- [20] Radbakhsh S, Najari M, Merimi M, *et al*. RNA modifications in osteoarthritis: epitranscriptomic insights into pathogenesis and therapeutic targets. *Int J Mol Sci*, 2025, **26**(10): 4955
- [21] Caire R, Audoux E, Courbon G, *et al*. YAP/TAZ: key players for rheumatoid arthritis severity by driving fibroblast like synovial cells phenotype and fibro-inflammatory response. *Front Immunol*, 2021, **12**: 791907
- [22] Lu M, Zhu M, Wu Z, *et al*. The role of YAP/TAZ on joint and arthritis. *FASEB J*, 2024, **38**(10): e23636
- [23] Wang N, Tytell J D, Ingber D E. Mechanotransduction at a distance: mechanically coupling the extracellular matrix with the nucleus. *Nat Rev Mol Cell Biol*, 2009, **10**(1): 75-82
- [24] Kechagia J Z, Ivaska J, Roca-Cusachs P. Integrins as biomechanical sensors of the microenvironment. *Nat Rev Mol Cell Biol*, 2019, **20**(8): 457-473
- [25] Atherton P, Stutchbury B, Wang D Y, *et al*. Vinculin controls Talin engagement with the actomyosin machinery. *Nat Commun*, 2015, **6**: 10038
- [26] Lee W, Nims R J, Savadipour A, *et al*. Inflammatory signaling sensitizes Piezo1 mechanotransduction in articular chondrocytes as a pathogenic feed-forward mechanism in osteoarthritis. *Proc Natl Acad Sci USA*, 2021, **118**(13): e2001611118
- [27] Panciera T, Azzolin L, Cordenonsi M, *et al*. Mechanobiology of YAP and TAZ in physiology and disease. *Nat Rev Mol Cell Biol*, 2017, **18**(12): 758-770
- [28] Bingle L, Singleton V, Bingle C D. The putative ovarian tumour marker gene *HE4* (WFDC2), is expressed in normal tissues and undergoes complex alternative splicing to yield multiple protein isoforms. *Oncogene*, 2002, **21**(17): 2768-2773
- [29] Liang L, Chen J, Di C, *et al*. Serum human epididymis protein 4 as

- a novel biomarker in identifying patients with interstitial lung disease in rheumatoid arthritis. *Front Med*, 2021, **8**: 755268
- [30] Xu Y, Wang J Y, Zou Y, *et al*. Role of IL-1 family cytokines IL-36, IL-37, IL-38 in osteoarthritis and rheumatoid arthritis: a comprehensive review. *J Inflamm Res*, 2024, **17**: 4001-4016
- [31] Wang K, Luo H, Liu L, *et al*. Blockade of IL-1 family cytokines in the treatment of rheumatoid arthritis. *Front Pharmacol*, 2025, **16**: 1577628
- [32] Wang Y, Yao M, Baker K B, *et al*. Force-dependent interactions between Talin and full-length Vinculin. *J Am Chem Soc*, 2021, **143**(36): 14726-14737
- [33] Humphries J D, Wang P, Streuli C, *et al*. Vinculin controls focal adhesion formation by direct interactions with Talin and actin. *J Cell Biol*, 2007, **179**(5): 1043-1057
- [34] Fisher L A B, Carriqui-Madroñal B, Mulder T, *et al*. Filamin protects myofibrils from contractile damage through changes in its mechanosensory region. *PLoS Genet*, 2024, **20**(6): e1011101
- [35] Goult B T, Yan J, Schwartz M A. Talin as a mechanosensitive signaling hub. *J Cell Biol*, 2018, **217**(11): 3776-3784
- [36] Razinia Z, Mäkelä T, Ylännä J, *et al*. Filamins in mechanosensing and signaling. *Annu Rev Biophys*, 2012, **41**: 227-246
- [37] Katoh K. Signal transduction mechanisms of focal adhesions: src and FAK-mediated cell response. *Front Biosci*, 2024, **29**(11): 392
- [38] Li Z, Shao R, Xin H, *et al*. Paxillin and kindlin: research progress and biological functions. *Biomolecules*, 2025, **15**(2): 173
- [39] Miki H, Manresa M C. Novel fibroblast phenotypes in homeostasis and chronic inflammation: from functions to potential regulators. *J Physiol*, 2023, **601**(12): 2273-2291
- [40] Roy T, Boateng S T, Uddin M B, *et al*. The PI3K-Akt-mTOR and associated signaling pathways as molecular drivers of immune-mediated inflammatory skin diseases: update on therapeutic strategy using natural and synthetic compounds. *Cells*, 2023, **12**(12): 1671
- [41] Humphries J D, Chastney M R, Askari J A, *et al*. Signal transduction via integrin adhesion complexes. *Curr Opin Cell Biol*, 2019, **56**: 14-21
- [42] Chastney M R, Conway J R W, Ivaska J. Integrin adhesion complexes. *Curr Biol*, 2021, **31**(10): R536-R542
- [43] Aplin J D, Ruane P T. Embryo-epithelium interactions during implantation at a glance. *J Cell Sci*, 2017, **130**(1): 15-22
- [44] He D, Liu X, Yang W, *et al*. The role of mechanosensitive ion channel Piezo1 in knee osteoarthritis inflammation. *Channels*, 2024, **18**(1): 2393088
- [45] Tian H, Chen L. Human Epididymis Protein 4 (HE4) as a promising biomarker and therapy target in fibrotic diseases: a review. *J Holist Integr Pharm*, 2024, **5**(4): 291-298
- [46] Keller J, O' Siorain J R, Kündig T M, *et al*. Molecular aspects of interleukin-36 cytokine activation and regulation. *Biochem Soc Trans*, 2024, **52**(4): 1591-1604
- [47] Sun Y, Leng P, Guo P, *et al*. G protein coupled estrogen receptor attenuates mechanical stress-mediated apoptosis of chondrocyte in osteoarthritis via suppression of Piezo1. *Mol Med*, 2021, **27**(1): 96
- [48] Wang N, Lu Y, Rothrauff B B, *et al*. Mechanotransduction pathways in articular chondrocytes and the emerging role of estrogen receptor- α . *Bone Res*, 2023, **11**(1): 13
- [49] Li M, Zhang F J, Bai R J. The hippo-YAP signaling pathway in osteoarthritis and rheumatoid arthritis. *J Inflamm Res*, 2024, **17**: 1105-1120
- [50] Frey S, Derer A, Messbacher M E, *et al*. The novel cytokine interleukin-36 α is expressed in psoriatic and rheumatoid arthritis synovium. *Ann Rheum Dis*, 2013, **72**(9): 1569-1574
- [51] Kanchanawong P, Calderwood D A. Organization, dynamics and mechanoregulation of integrin-mediated cell-ECM adhesions. *Nat Rev Mol Cell Biol*, 2023, **24**(2): 142-161
- [52] Zhu L, Plow E F, Qin J. Initiation of focal adhesion assembly by Talin and kindlin: a dynamic view. *Protein Sci*, 2021, **30**(3): 531-542
- [53] Ripamonti M, Wehrle-Haller B, de Curtis I. Paxillin: a hub for mechano-transduction from the $\beta 3$ integrin-Talin-kindlin axis. *Front Cell Dev Biol*, 2022, **10**: 852016
- [54] Katsuta H, Sokabe M, Hirata H. From stress fiber to focal adhesion: a role of actin crosslinkers in force transmission. *Front Cell Dev Biol*, 2024, **12**: 1444827
- [55] Ridone P, Vassalli M, Martinac B. Piezo1 mechanosensitive channels: what are they and why are they important. *Biophys Rev*, 2019, **11**(5): 795-805
- [56] Wang J, Jing F, Zhao Y, *et al*. Piezo1: structural pharmacology and mechanotransduction mechanisms. *Trends Pharmacol Sci*, 2025, **46**(8): 752-770
- [57] Puntillo F, Giglio M, Corriero A, *et al*. Unraveling the joints: a narrative review of osteoarthritis. *Eur Rev Med Pharmacol Sci*, 2024, **28**(15): 4080-4104
- [58] Ouyang Z, Dong L, Yao F, *et al*. Cartilage-related collagens in osteoarthritis and rheumatoid arthritis: from pathogenesis to therapeutics. *Int J Mol Sci*, 2023, **24**(12): 9841
- [59] Hu T, Zhang Z, Deng C, *et al*. Effects of $\beta 2$ integrins on osteoclasts, macrophages, chondrocytes, and synovial fibroblasts in osteoarthritis. *Biomolecules*, 2022, **12**(11): 1653
- [60] Jin H, Jiang S, Wang R, *et al*. Mechanistic insight into the roles of integrins in osteoarthritis. *Front Cell Dev Biol*, 2021, **9**: 693484
- [61] Lu F, Zhu L, Bromberger T, *et al*. Mechanism of integrin activation by Talin and its cooperation with kindlin. *Nat Commun*, 2022, **13**(1): 2362
- [62] Wu X, Lai Y, Chen S, *et al*. Kindlin-2 preserves integrity of the articular cartilage to protect against osteoarthritis. *Nat Aging*, 2022, **2**(4): 332-347
- [63] Calderwood D A, Campbell I D, Critchley D R. Talins and kindlins: partners in integrin-mediated adhesion. *Nat Rev Mol Cell Biol*, 2013, **14**(8): 503-517
- [64] Katoh K. Integrin and its associated proteins as a mediator for mechano-signal transduction. *Biomolecules*, 2025, **15**(2): 166
- [65] Ma X, Hammes S R. Paxillin actions in the nucleus. *Steroids*, 2018, **133**: 87-92
- [66] Shahrara S, Castro-Rueda H P, Haines G K, *et al*. Differential expression of the FAK family kinases in rheumatoid arthritis and osteoarthritis synovial tissues. *Arthritis Res Ther*, 2007, **9**(5): R112
- [67] Deakin N O, Turner C E. Paxillin comes of age. *J Cell Sci*, 2008, **121**(15): 2435-2444
- [68] Shirinsky V S, Kazygasheva E V, Shirinsky I V. Inflammation and immunity: a role of pathogenesis of osteoarthritis. *Med Immunol*, 2019, **21**(1): 39-48
- [69] Harre U, Schett G. Cellular and molecular pathways of structural damage in rheumatoid arthritis. *Semin Immunopathol*, 2017, **39**(4): 355-363
- [70] Gao W, Hasan H, Anderson D E, *et al*. The role of mechanically-activated ion channels Piezo1, Piezo2, and TRPV4 in chondrocyte mechanotransduction and mechano-therapeutics for

- osteoarthritis. *Front Cell Dev Biol*, 2022, **10**: 885224
- [71] Yang B, Ma D, Zhu X, *et al*. Roles of TRP and PIEZO receptors in autoimmune diseases. *Expert Rev Mol Med*, 2024, **26**: e10
- [72] James N E, Emerson J B, Borgstadt A D, *et al*. The biomarker *HE4* (*WFDC2*) promotes a pro-angiogenic and immunosuppressive tumor microenvironment *via* regulation of *STAT3* target genes. *Sci Rep*, 2020, **10**(1): 8558
- [73] Murrieta-Coxca J M, Rodríguez-Martínez S, Cancino-Díaz M E, *et al*. IL-36 cytokines: regulators of inflammatory responses and their emerging role in immunology of reproduction. *Int J Mol Sci*, 2019, **20**(7): 1649
- [74] Striz I. Cytokines of the IL-1 family: recognized targets in chronic inflammation underrated in organ transplantations. *Clin Sci*, 2017, **131**(17): 2241-2256
- [75] Haining A W M, Lieberthal T J, Del Río Hernández A. Talin: a mechanosensitive molecule in health and disease. *FASEB J*, 2016, **30**(6): 2073-2085
- [76] Kong L, Wang B, Yang X, *et al*. Integrin-associated molecules and signalling cross talking in osteoclast cytoskeleton regulation. *J Cell Mol Med*, 2020, **24**(6): 3271-3281
- [77] Lauer J C, Selig M, Hart M L, *et al*. Articular chondrocyte phenotype regulation through the cytoskeleton and the signaling processes that originate from or converge on the cytoskeleton: towards a novel understanding of the intersection between actin dynamics and chondrogenic function. *Int J Mol Sci*, 2021, **22**(6): 3279
- [78] Neofotistou-Themeli E, Goutakoli P, Chanis T, *et al*. Fibroblasts in rheumatoid arthritis: novel roles in joint inflammation and beyond. *Front Med*, 2025, **11**: 1376925
- [79] Liu Y, Jia F, Li K, *et al*. Critical signaling molecules in the temporomandibular joint osteoarthritis under different magnitudes of mechanical stimulation. *Front Pharmacol*, 2024, **15**: 1419494
- [80] Gehwolf R, Tempfer H, Cesur N P, *et al*. Tendinopathy: the interplay between mechanical stress, inflammation, and vascularity. *Adv Sci*, 2025, **12**(36): e06440
- [81] Chen S, Li Z, Zhang J, *et al*. Piezo1 at the crossroads: mediating inflammation and mechanical stress in joint disorders. *Joint Bone Spine*, 2025, **93**(2): 105953
- [82] Zhang Y, Zhuang H, Ren X, *et al*. Implications of mechanosensitive ion channels in the pathogenesis of osteoarthritis: a comprehensive review. *Front Cell Dev Biol*, 2025, **13**: 1549812
- [83] Zheng S, Wang H, Mu J, *et al*. Macrophage-centred crosstalk with infiltrating immune cells in rheumatoid arthritis and its regulation by mesenchymal stem cells. *J Transl Med*, 2025, **23**(1): 1360
- [84] Mitrović J, Hrkač S, Tečler J, *et al*. Pathogenesis of extraarticular manifestations in rheumatoid arthritis-a comprehensive review. *Biomedicines*, 2023, **11**(5): 1262
- [85] Yu Z, Nian C, Sun W, *et al*. Elevated serum HE4 levels as a novel biomarker of disease severity and hepatic fibrosis in autoimmune hepatitis. *Clin Chim Acta*, 2024, **559**: 119682
- [86] Lan Y, Lu J, Zhang S, *et al*. Piezo1-mediated mechanotransduction contributes to disturbed flow-induced atherosclerotic endothelial inflammation. *J Am Heart Assoc*, 2024, **13**(21): e035558
- [87] Yang Y, Wang D, Zhang C, *et al*. Piezo1 mediates endothelial atherogenic inflammatory responses *via* regulation of YAP/TAZ activation. *Hum Cell*, 2022, **35**(1): 51-62
- [88] Boutet M A, Nerviani A, Pitzalis C. IL-36, IL-37, and IL-38 cytokines in skin and joint inflammation: a comprehensive review of their therapeutic potential. *Int J Mol Sci*, 2019, **20**(6): 1257
- [89] Troeberg L, Nagase H. Proteases involved in cartilage matrix degradation in osteoarthritis. *Biochim Biophys Acta*, 2012, **1824**(1): 133-45
- [90] Little C B, Fosang A J. Is cartilage matrix breakdown an appropriate therapeutic target in osteoarthritis—insights from studies of aggrecan and collagen proteolysis?. *Curr Drug Targets*, 2010, **11**(5): 561-575
- [91] Mierke C T. Extracellular matrix cues regulate mechanosensing and mechanotransduction of cancer cells. *Cells*, 2024, **13**(1): 96
- [92] Yuan Z C, Xu W D, Liu X Y, *et al*. Biology of IL-36 signaling and its role in systemic inflammatory diseases. *Front Immunol*, 2019, **10**: 2532
- [93] Chatterjee A, Tumarín J, Prabhakar S. Cellular cross-talk drives mesenchymal transdifferentiation in diabetic kidney disease. *Front Med*, 2025, **11**: 1499473
- [94] Banerjee S, Nara R, Chakraborty S, *et al*. Integrin regulated autoimmune disorders: understanding the role of mechanical force in autoimmunity. *Front Cell Dev Biol*, 2022, **10**: 852878
- [95] Ganesan R, Rasool M. Fibroblast-like synoviocytes-dependent effector molecules as a critical mediator for rheumatoid arthritis: current status and future directions. *Int Rev Immunol*, 2017, **36**(1): 20-30
- [96] Guo L, Wang J, Li J, *et al*. Biomarkers of rheumatoid arthritis-associated interstitial lung disease: a systematic review and meta-analysis. *Front Immunol*, 2024, **15**: 1455346
- [97] Zhao Y, Wang J, Xu L, *et al*. Beyond bone loss: a biology perspective on osteoporosis pathogenesis, multi-omics approaches, and interconnected mechanisms. *Biomedicines*, 2025, **13**(6): 1443
- [98] Pianta A, Drouin E E, Wang Q, *et al*. OP0116 identification of N-acetylglucosamine-6-sulfatase and filamin A as novel targets of autoimmune T and B cell responses in rheumatoid arthritis. *Ann Rheum Dis*, 2015, **74**: 112
- [99] Connolly M, Veale D J, Fearon U. Acute serum amyloid A regulates cytoskeletal rearrangement, cell matrix interactions and promotes cell migration in rheumatoid arthritis. *Ann Rheum Dis*, 2011, **70**(7): 1296-1303
- [100] Xu X, Tang H, Zhang S, *et al*. The role(s) of HE4 and other WAP factors for sperm functions and male urogenital diseases. *Biol Reprod*, 2025, **113**(1): 8-18
- [101] He C, Li Q, Huang R, *et al*. Pain phenotype in knee osteoarthritis: implications for mechanism-based therapy. *Orthop Surg*, 2025, **17**(11): 3007-3021
- [102] Cajas L J, Casallas A, Medina Y F, *et al*. Pannus and rheumatoid arthritis: historic and pathophysiological evolution. *Rev Colomb De Reumatologia Engl Ed*, 2019, **26**(2): 118-128
- [103] Guo Q, Wang Y, Xu D, *et al*. Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. *Bone Res*, 2018, **6**: 15
- [104] Li Z, Hao L, Chen S, *et al*. Forkhead box C1 promotes the pathology of osteoarthritis in subchondral bone osteoblasts *via* the Piezo1/YAP axis. *Cell Signal*, 2024, **124**: 111463
- [105] Kamiya H, Panlaqui O M. Systematic review and meta-analysis of the risk of rheumatoid arthritis-associated interstitial lung disease related to anti-cyclic citrullinated peptide (CCP) antibody. *BMJ Open*, 2021, **11**(3): e040465
- [106] Zhang H, Ye Y, Ling X, *et al*. The role of IL-37 and IL-38 in

- rheumatoid arthritis, the potential clinical applications in precision medicine. *Front Immunol*, 2025, **16**: 1629759
- [107] Lucius K. Novel and emerging markers of chronic or low-grade inflammation. *Integr Complementary Ther*, 2023, **29**(3): 130-142
- [108] Ahmed S A, Darwish E M, Attia W A, *et al.* Anti-carbamylated protein antibodies and serum level of 14-3-3 protein for early detection of rheumatoid arthritis patient in correlation with rheumatoid factor, anti-CCP antibodies, disease activity and joint damage using high frequency musculoskeletal ultrasound. *Appl Clin Res Clin Trials Regul Aff*, 2020, **7**(2): 141-153
- [109] Alharthi A H, Al-Shehri S H A, Albarqi M A A, *et al.* Laboratory markers of inflammation: CRP and ESR in clinical practice. *Journal of International Crisis and Risk Communication Research*, 2024, **7**(Suppl8): 2376
- [110] Liu Y, Zhang Z, Li J, *et al.* Piezo1 transforms mechanical stress into pro senescence signals and promotes osteoarthritis severity. *Mech Ageing Dev*, 2023, **216**: 111880
- [111] Huang Y, Sun H, Chen H, *et al.* Mechanical load-induced upregulation of Talin2 through non-canonical deubiquitination of OTUB1 drives facet joint osteoarthritis pathogenesis. *Adv Sci*, 2025, **12**(25): 2501046
- [112] Pianta A, Arvikar S L, Strle K, *et al.* Two rheumatoid arthritis-specific autoantigens correlate microbial immunity with autoimmune responses in joints. *J Clin Invest*, 2017, **127**(8): 2946-2956
- [113] Doskaliuk B, Zaiats L, Sahan N, *et al.* The fibrosis puzzle of systemic sclerosis-associated ILD and the quest for targeted interventions. *Ther Adv Respir Dis*, 2025, **19**: 17534666251366023
- [114] Jiang L, Fang X G, Lan P M, *et al.* Correlation analysis of serum HE4 and PS-PLA1 expression with disease activity and disease outcome in patients with rheumatoid arthritis. *J Bengbu Med Univ*, 2024, **49**(11): 1463-1466
- [115] Boutet M A, Bart G, Penhoat M, *et al.* Distinct expression of interleukin (IL)-36 α , β and γ , their antagonist IL-36Ra and IL-38 in psoriasis, rheumatoid arthritis and Crohn's disease. *Clin Exp Immunol*, 2016, **184**(2): 159-173
- [116] Liu K, Zhang B, Zhang X. Promoting articular cartilage regeneration through microenvironmental regulation. *J Immunol Res*, 2024, **2024**: 4751168
- [117] Zhou W, Shen Q, Wang H, *et al.* Knockdown of YAP/TAZ inhibits the migration and invasion of fibroblast synovial cells in rheumatoid arthritis by regulating autophagy. *J Immunol Res*, 2020, **2020**: 9510594
- [118] Chu C Q. Highlights of strategies targeting fibroblasts for novel therapies for rheumatoid arthritis. *Front Med*, 2022, **9**: 846300
- [119] Zhang X Y, Hong L L, Ling Z Q. MUC16: clinical targets with great potential. *Clin Exp Med*, 2024, **24**(1): 101
- [120] Feng H, Ang K, Guan P, *et al.* Application of adhesives in the treatment of cartilage repair. *Interdiscip Med*, 2024, **2**(4): e20240015
- [121] Dieterle M P, Husari A, Rolauffs B, *et al.* Integrins, cadherins and channels in cartilage mechanotransduction: perspectives for future regeneration strategies. *Expert Rev Mol Med*, 2021, **23**: e14
- [122] Di Sario G, Rossella V, Famulari E S, *et al.* Enhancing clinical potential of liquid biopsy through a multi-omic approach: a systematic review. *Front Genet*, 2023, **14**: 1152470
- [123] Soundararajan A, Wang T, Sundararajan R, *et al.* Multiomics analysis reveals the mechanical stress-dependent changes in trabecular meshwork cytoskeletal-extracellular matrix interactions. *Front Cell Dev Biol*, 2022, **10**: 874828
- [124] Sammut S J, Crispin-Ortuzar M, Chin S F, *et al.* Multi-omic machine learning predictor of breast cancer therapy response. *Nature*, 2022, **601**(7894): 623-629
- [125] Virdi J K, Pethe P. Biomaterials regulate mechanosensors YAP/TAZ in stem cell growth and differentiation. *Tissue Eng Regen Med*, 2021, **18**(2): 199-215
- [126] Yi Y H, Chen G, Gong S, *et al.* Injectable temperature-sensitive hydrogel loaded with IL-36Ra for the relief of osteoarthritis. *ACS Biomater Sci Eng*, 2023, **9**(3): 1672-1681
- [127] Pirri C. Exploring the revolutionary impact of YAP pathways on physical and rehabilitation medicine. *Biomolecules*, 2025, **15**(1): 96
- [128] Catapano M, Vergnano M, Romano M, *et al.* IL-36 promotes systemic IFN-I responses in severe forms of psoriasis. *J Invest Dermatol*, 2020, **140**(4): 816-826.e3
- [129] Zhou Y, Li M, Lin S, *et al.* Mechanical sensing protein PIEZO1 controls osteoarthritis via glycolysis mediated mesenchymal stem cells-Th17 cells crosstalk. *Cell Death Dis*, 2025, **16**(1): 231
- [130] Knecht R S, Bucher C H, Van Linthout S, *et al.* Mechanobiological principles influence the immune response in regeneration: implications for bone healing. *Front Bioeng Biotechnol*, 2021, **9**: 614508
- [131] Nateghi R, Zhou R, Saft M, *et al.* Artificial intelligence (AI)-driven screening of equivocal prostate immunohistochemistry (IHC) cases: development and validation of a screening and cancer detection framework. *Mod Pathol*, 2025, **38**(12): 100904
- [132] Schmauch B, Cabeli V, Domingues O D, *et al.* Deep learning uncovers histological patterns of YAP1/TEAD activity related to disease aggressiveness in cancer patients. *iScience*, 2024, **28**(1): 111638
- [133] Yang J, Xu C, Xie X, *et al.* Roles of Piezo1 in chronic inflammatory diseases and prospects for drug treatment (Review). *Mol Med Rep*, 2025, **32**(1). <http://doi.org/10.3892/mmr.2025.13565>
- [134] Wang Z, Wang J, Lan T, *et al.* Role and mechanism of fibroblast-activated protein- α expression on the surface of fibroblast-like synoviocytes in rheumatoid arthritis. *Front Immunol*, 2023, **14**: 1135384
- [135] Andoh A, Nishida A. Pro- and anti-inflammatory roles of interleukin (IL)-33, IL-36, and IL-38 in inflammatory bowel disease. *J Gastroenterol*, 2023, **58**(2): 69-78
- [136] Talukdar P D, Roy H, Chatterji U. Targeting breast cancer stem cells in ER-positive breast cancer by repurposing the benzoporphyrin derivative verteporfin as a YAP/TAZ small molecule inhibitor. *Mol Biol Rep*, 2025, **52**(1): 154
- [137] Zhang C, He H, Li X, *et al.* The role of piezo-type mechanosensitive ion channel component 1 in inflammatory bowel disease. *J Innate Immun*, 2025, **17**(1): 1
- [138] Zhang Y T, Li H H, Teng F. Inhibition of Piezo1 ameliorates septic cardiomyopathy by blocking calcium-dependent PANoptosis. *Eur J Pharmacol*, 2025, **996**: 177438
- [139] Brouwer N J, Konstantinou E K, Gragoudas E S, *et al.* Targeting the YAP/TAZ pathway in uveal and conjunctival melanoma with verteporfin. *Invest Ophthalmol Vis Sci*, 2021, **62**(4): 3
- [140] Barrette A M, Ronk H, Joshi T, *et al.* Anti-invasive efficacy and survival benefit of the YAP-TEAD inhibitor verteporfin in preclinical glioblastoma models. *Neuro Oncol*, 2022, **24**(5): 694-707

- [141] Haghshenas M R, Zamir M R, Sadeghi M, *et al*. Clinical relevance and therapeutic potential of IL-38 in immune and non-immune-related disorders. *Eur Cytokine Netw*, 2022, **33**(3): 54-69
- [142] Liu J, Deng Y, Yan J. Decoding force-transmission linkages for therapeutic targeting and engineering. *APL Bioeng*, 2025, **9**(2): 021504
- [143] Nakamura F. The role of mechanotransduction in contact inhibition of locomotion and proliferation. *Int J Mol Sci*, 2024, **25**(4): 2135
- [144] Pang X, He X, Qiu Z, *et al*. Targeting integrin pathways: mechanisms and advances in therapy. *Signal Transduct Target Ther*, 2023, **8**(1): 1
- [145] Seo B R, Mooney D J. Recent and future strategies of mechanotherapy for tissue regenerative rehabilitation. *ACS Biomater Sci Eng*, 2022, **8**(11): 4639-4642
- [146] Melton E, Qiu H. Interleukin-36 cytokine/receptor signaling: a new target for tissue fibrosis. *Int J Mol Sci*, 2020, **21**(18): 6458
- [147] Nordberg R C, Bielajew B J, Takahashi T, *et al*. Recent advancements in cartilage tissue engineering innovation and translation. *Nat Rev Rheumatol*, 2024, **20**(6): 323-346
- [148] Manzari M T, Shamay Y, Kiguchi H, *et al*. Targeted drug delivery strategies for precision medicines. *Nat Rev Mater*, 2021, **6**(4): 351-370
- [149] Wang X, Tao J, Zhou J, *et al*. Excessive load promotes temporomandibular joint chondrocyte apoptosis *via* Piezo1/endoplasmic reticulum stress pathway. *J Cell Mol Med*, 2024, **28**(11): e18472
- [150] Calabrese L, Fiocco Z, Satoh T K, *et al*. Therapeutic potential of targeting interleukin-1 family cytokines in chronic inflammatory skin diseases. *Br J Dermatol*, 2022, **186**(6): 925-941
- [151] Korovina M O, Valeeva A R, Akhtyamov I F, *et al*. Joint tissues: convergence and divergence of the pathogenetic mechanisms of rheumatoid arthritis and osteoarthritis. *Int J Mol Sci*, 2025, **26**(17): 8742
- [152] Börjesson A E, Lagerquist M K, Windahl S H, *et al*. The role of estrogen receptor α in the regulation of bone and growth plate cartilage. *Cell Mol Life Sci*, 2013, **70**(21): 4023-4037
- [153] Hwang J, Rick J, Hsiao J, *et al*. A review of IL-36: an emerging therapeutic target for inflammatory dermatoses. *J Dermatolog Treat*, 2022, **33**(6): 2711-2722
- [154] Burden A D. Spesolimab, an interleukin-36 receptor monoclonal antibody, for the treatment of generalized pustular psoriasis. *Expert Rev Clin Immunol*, 2023, **19**(5): 473-481
- [155] Sun H, Ying M. Abstract 4444: Small molecule drug Verteporfin inhibits TAZ/YAP-driven signaling and tumorigenicity of breast cancer cells. *Cancer Res*, 2015, **75**(15_Supplement): 4444
- [156] Read R D. Repurposing the drug verteporfin as anti-neoplastic therapy for glioblastoma. *Neuro Oncol*, 2022, **24**(5): 708-710
- [157] Cheng C H, Chen L R, Chen K H. Osteoporosis due to hormone imbalance: an overview of the effects of estrogen deficiency and glucocorticoid overuse on bone turnover. *Int J Mol Sci*, 2022, **23**(3): 1376
- [158] Kwon Y. YAP/TAZ as molecular targets in skeletal muscle atrophy and osteoporosis. *Aging Dis*, 2024, **16**(1): 299-320