Cell Signaling

Zhang C, et al., Cell Signal.
2026;4(1):105-110.

Commentary

Beyond cytokines: Paradigm shift towards mechano-chemical signaling circuits in psoriasis and inflammatory dermatoses

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Received date: April 15, 2026
Accepted date: June 29, 2026

Abstract

Psoriasis represents a classic immune-mediated chronic inflammatory skin disorder with widespread global prevalence. Traditional research frameworks center on the IL-23/Th17 immune cascade to explain bidirectional communication between immune cells and epidermal keratinocytes, while the mechanical regulatory functions of dermal extracellular matrix microenvironment have long been overlooked. A recently proposed mechano-chemical signaling axis starts with dendritic cell-derived galectin-9, which acts on CD44-expressing papillary fibroblasts to trigger excessive collagen deposition and pathological stiffening at the dermal-epidermal junction. Such mechanical tissue alterations further activate downstream intracellular signaling cascades in basal keratinocytes, driving persistent epidermal hyperproliferation via sequential HMGB2 and RRM2 upregulation. Rather than serving as a direct mechanical sensor, HMGB2 acts as a downstream transcriptional effector whose nuclear translocation and expression levels are controlled by matrix stiffness-dependent mechanotransduction signals including YAP/TAZ. This paper systematically dissects the multi-layered molecular logic of this cross-tissue chemical-mechanical signaling circuit and compares its potential conserved pathological roles across atopic dermatitis, systemic sclerosis and cutaneous squamous cell carcinoma. We further summarize major methodological and translational limitations of existing research, such as insufficient age and sex stratification in preclinical and human tissue studies, and the lack of direct *in vivo* evidence supporting mechanical positive feedback loops in psoriatic lesions. Distinct from conventional single-target anti-cytokine regimens, we put forward a novel dual therapeutic strategy combining anti-inflammatory and localized anti-fibrotic interventions for refractory inflammatory skin diseases, avoiding systemic toxicities caused by broad-spectrum anti-fibrotic agents. Targeting cell-matrix mechanotransduction interfaces provides a promising direction for developing durable treatments for intractable inflammatory dermatoses.

Keywords: Psoriasis, Mechanobiology, Extracellular matrix stiffness, LGALS9, Fibroblasts, Mechanotransduction

Introduction

Inflammatory skin diseases, particularly psoriasis, have long been conceptualized as disorders fundamentally driven by immune dysregulation [1,2]. The canonical signaling model envisions a linear pathway in which professional immune cells-including plasmacytoid DCs and T lymphocytes-secrete a battery of pro-inflammatory cytokines (IL-17A, IL-22, IL-23, TNF-α), which traverse the DEJ as soluble chemical signals to act directly on epidermal keratinocytes, inducing their aberrant proliferation and differentiation [3–8].

This linear model, however, neglects the fundamental physical nature of the skin as a structural organ. The skin is the body's largest barrier tissue, constantly subjected to multiaxial mechanical

forces including tension, compression, and shear [9,10]. The burgeoning field of mechanobiology has revealed that cells sense and respond to their physical microenvironment through mechanosensory elements such as integrins, focal adhesion kinase (FAK), and cytoskeletal remodeling pathways [11,12], thereby governing cell fate decisions, gene expression programs, and disease progression [13,14]. Abnormal DEJ stiffness in psoriatic lesions has been preliminarily documented [15], yet its upstream driving mechanisms and downstream functional consequences have long remained unresolved.

The work of Jiang *et al*. [5] emerges as a seminal contribution at the intersection of mechanobiology and psoriasis pathobiology. It demonstrates that in the psoriatic disease process, a chemical signal (LGALS9) can induce changes in the physical microenvironment (elevated ECM stiffness), and that this physical alteration itself constitutes a critical signal driving pathological epidermal hyperproliferation. This "mechano-chemical" coupling perspective not only challenges the traditional "chemical-dominant" pathological paradigm but fundamentally redefines dermal fibroblasts, from passive collagen manufacturers to active mechano-chemical signal processors, providing new coordinates for understanding the multidimensional complexity of inflammatory signal transduction.

Building on a systematic account of the LGALS9-CD44-HMGB2-RRM2 core circuit, this paper further explores its mechanistic generalizability across related dermatoses, and proposes a "dual anti-inflammatory and anti-fibrotic" combinatorial framework prioritizing local lesion-targeted intervention for refractory inflammatory skin diseases.

The Core Signaling Circuit: LGALS9-CD44-HMGB2-RRM2

In psoriatic lesions, infiltrating DCs — particularly CD11c+ subsets within the papillary dermis, represents a principal source of initiating inflammatory signals [16,17]. Jiang *et al*. specifically identified that these DCs selectively secrete galectin-9 (Galectin-9, LGALS9), a secreted lectin harboring tandem carbohydrate-recognition domains whose immunomodulatory and pro-fibrotic effects have been validated in human skin and systemic fibrotic disorders [18,19,34]. Within the psoriatic pathological context, LGALS9 functions as a critical "chemical-to-physical signal transducer," relaying immune activation signals to adjacent stromal cells and thereby initiating the downstream mechanical signaling cascade.

The pathological effects of LGALS9 are not mediated by direct action on keratinocytes, but through dermal fibroblasts functioning as obligatory signal intermediaries. Notably, this response is not a property of all dermal fibroblasts but is specifically executed by a CD44-high expressing subpopulation residing in the papillary dermis, immediately adjacent to the DEJ [5,20]. This spatial specificity is biologically meaningful: the anatomical positioning of papillary fibroblasts ensures precise signal relay to the overlying epidermal basal layer, rather than diffuse effects throughout the bulk dermis.

CD44, a cell surface receptor for hyaluronic acid and numerous glycoproteins including LGALS9, plays a central role in mediating cell-matrix interactions [21]. LGALS9-CD44 engagement triggers activation of papillary dermal fibroblasts, inducing overproduction and deposition of type I, III, and VI collagens [5]. This "chemical-to-physical" conversion transforms ligand-receptor chemical signals into changes in tissue mechanical properties, constituting the pivotal nexus of the entire signaling cascade.

Excessive collagen deposition results in a significant increase in ECM stiffness at the DEJ, quantifiable by high-resolution mechanical methods such as atomic force microscopy (AFM) [15,22]. This elevated matrix stiffness is sensed by epidermal basal keratinocytes through integrins, particularly the α6β4 and αvβ5 heterodimers [23]. As transmembrane mechanosensors, integrins convert ECM physical signals into intracellular biochemical cascades, activating FAK, Rho GTPases, and downstream cytoskeletal remodeling programs [12,14].

Matrix stiffness further regulates the nucleocytoplasmic shuttling of mechano-sensitive transcriptional co-activators YAP/TAZ through the integrin-FAK-YAP/TAZ axis, thereby reprogramming cellular gene expression programs governing proliferation, collagen synthesis and inflammatory mediator release. As master mechanotransduction hubs, YAP/TAZ transduce integrin-cytoskeleton mechanical inputs into transcriptional outputs in both papillary fibroblasts and epidermal keratinocytes, yet their hierarchical relationship with HMGB2 remains incompletely resolved in psoriatic lesions. Three non-exclusive mechanistic models can be proposed based on existing mechanobiology and the findings of Jiang *et al*.

HMGB2 functions as a downstream transcriptional effector of YAP/TAZ: Elevated matrix stiffness promotes nuclear translocation of YAP/TAZ, which directly binds the promoter/enhancer regions of HMGB2 to upregulate its gene transcription; nuclear HMGB2 subsequently amplifies RRM2 expression to drive basal keratinocyte hyperproliferation.

HMGB2 operates in parallel, independent of YAP/TAZ: Mechanical signals bifurcate downstream of integrin-FAK: one branch activates YAP/TAZ canonical mechanotransduction, while a separate kinase cascade mediates post-translational modification and nuclear enrichment of HMGB2, with both axes synergistically promoting epidermal overgrowth.

Cooperative cross-talk between YAP/TAZ and HMGB2: Nuclear YAP/TAZ and HMGB2 form a transcriptional complex to co-regulate the RRM2 locus, generating a multiplicative proliferative response under pathological tissue stiffening.

At present, Jiang *et al*.'s dataset does not provide direct chromatin binding or genetic epistasis evidence to discriminate these models. Resolving whether HMGB2 lies downstream, parallel to, or cooperatively with YAP/TAZ is not merely a mechanistic detail but a foundational prerequisite for target prioritization: selective YAP/TAZ inhibitors would broadly block matrix stiffness-driven transcriptional programs, while HMGB2 neutralization would specifically intercept the terminal proliferative effector without pan-mechanobiological suppression. Future combinatorial genetic perturbation assays in ex vivo human skin organoids and IMQ mouse models are required to dissect this regulatory hierarchy.

Mechanical signals transduced via integrin-FAK-YAP/TAZ signaling drive transcriptional upregulation and nuclear translocation of high mobility group box protein 2 (HMGB2) [5]. Conventionally regarded as a chromatin-binding protein and extracellular inflammatory alarmin [24], HMGB2 expression and

nuclear localization are regulated by matrix stiffness rather than directly sensing mechanical force itself. This substantially expands our understanding of its functional repertoire: HMGB2 is not only a responder to chemical inflammation but also a downstream effector of tissue mechanical signals. HMGB2 subsequently upregulates ribonucleotide reductase M2 (RRM2), the rate-limiting enzyme for DNA synthesis, whose sustained overactivation ultimately drives aberrant proliferation of epidermal basal cells [5,25].

This complete signaling chain: DCs (LGALS9) to papillary fibroblasts (CD44-ECM remodeling), to basal keratinocytes (integrin-FAK-YAP/TAZ-HMGB2-RRM2), dismantles the traditional dogma of "direct dialogue" between immune cells and keratinocytes, establishing fibroblasts as the central "mechano-chemical signal relay station."

Signal "Dual Encoding": Molecular Basis of Chemical-to-Mechanical Signal Conversion

Conventional signal transduction research focuses on phosphorylation cascades or transcription factor activation — inherently chemical processes. The work of Jiang *et al*. exemplifies a paradigmatic "signal modality switching" event. Between the engagement of LGALS9 and CD44 (chemical signal input) and the hyperproliferation of keratinocytes (effector output), there is a physical signal intermediate, namely the alteration of extracellular matrix stiffness, which forms a rare "chemical-physical-chemical" trimodal encoding architecture in signal transduction.

The molecular basis of this conversion involves multiple processes. Following CD44 activation, fibroblasts undergo transcriptomic reprogramming, markedly upregulating collagen synthesis genes (COL1A1, COL3A1, COL6A1). Secreted collagen molecules are subsequently cross-linked extracellularly by lysyl oxidase (LOX) and related enzymes, forming a highly cross-linked rigid collagen network [26,27], completing the full transmodal conversion from chemical signals to physical stiffness.

From the perspective of downstream mechanical signal propagation, in addition to the integrin-FAK-YAP/TAZ pathway, the cytoskeletal tension-MRTF-A/SRF pathway merits attention: elevated matrix stiffness promotes G-actin to F-actin polymerization, activating MRTF-A-mediated transcriptional programs [28]. The precise molecular mechanism coupling HMGB2 activation to these mechanosensing pathways awaits further elucidation; however, existing evidence sufficiently establishes that matrix physical state constitutes an independent variable governing nuclear transcriptional activity, irreducible to a mere surrogate of chemical signaling.

Mechanistic Generalizability: Potential Roles of the Mechano-Chemical Circuit in Related Inflammatory Dermatoses

Atopic dermatitis

Atopic dermatitis (AD) is the most prevalent allergic skin disease, with chronic-phase lichenification characterized by prominent dermal fibrosis and epidermal thickening [29]. While AD's immunological bias (Th2/Th22-dominant) is fundamentally distinct from psoriasis (Th17/Th1-dominant), the question of whether ECM stiffening during lichenification can similarly activate keratinocyte hyperproliferation through analogous mechanical signaling pathways represents a scientifically compelling inquiry. Preliminary evidence suggests that CD44 upregulation and fibroblast activation participate in lichenification formation in chronic AD lesions [30], implying that the LGALS9-CD44-ECM axis may harbor cross-indication mechanistic commonalities, with differences potentially confined to upstream inflammatory drivers rather than the fundamental logic of downstream mechanotransduction.

Systemic sclerosis

Systemic sclerosis (SSc, scleroderma) is an autoimmune disease characterized by excessive ECM deposition and progressive fibrosis [31]. Although its initiating mechanisms differ from psoriasis, LGALS9 expression is markedly elevated in lesional skin of SSc patients and positively correlates with skin fibrosis severity [10], suggesting the DC-LGALS9-CD44 fibroblast axis may represent a shared upstream fibrotic trigger across inflammatory skin disorders. More critically, progressive ECM stiffening in SSc acts as a positive feedback signal that reactivates fibroblasts via integrin-FAK signaling, forming a well-documented self-reinforcing fibrotic vicious cycle: "stiffness increase–fibroblast activation–enhanced collagen deposition–further matrix stiffening". By analogy, an analogous mechanochemical positive feedback loop is a testable but unvalidated hypothesis for psoriatic plaques. To formally confirm whether tissue stiffening drives sustained inflammation, chronic lesion persistence, or disease relapse in psoriasis, longitudinal *in vivo* stiffness tracking paired with targeted mechanical perturbation assays (e.g., local ECM softening interventions) in IMQ murine models and serial human psoriatic biopsy cohorts are mandatory. At present, no direct human or preclinical psoriatic tissue data confirms that this mechanical feedback axis contributes to disease chronicity. This provides clear theoretical grounding for anti-fibrotic strategies targeting the mechanical sensing interface.

Cutaneous squamous cell carcinoma

Psoriasis harbors tumor-like proliferative characteristics, and psoriatic patients face an elevated risk of developing cutaneous squamous cell carcinoma (cSCC). Tumor mechanobiology research has conclusively established that matrix stiffness is a major driver of tumor cell proliferation, invasion, and chemoresistance [13]. During the transition from psoriasis to cSCC, the HMGB2-RRM2 axis may constitute a pivotal molecular node linking inflammatory and neoplastic proliferation: HMGB2 participates in chromatin remodeling, while sustained RRM2 overactivation may induce replication stress and genomic instability, providing a molecular substrate for neoplastic transformation [25,33]. If validated, this hypothesis would reveal a mechano-proliferative common mechanism underlying the link between chronic inflammation and cutaneous carcinogenesis.

Research Limitations and Methodological Reflections

Despite its paradigm-shifting significance, several important limitations of Jiang *et al*. warrant consideration.

Animal model extrapolation

The study was primarily based on the imiquimod (IMQ)-induced murine psoriasis model, which principally recapitulates acute IL-23/Th17-driven psoriasiform lesions. It cannot fully replicate the pathological features of chronic human psoriasis, particularly with respect to the degree of dermal fibrosis, fibroblast subpopulation distribution, and DEJ biophysical properties. Whether LGALS9-

CD44-driven ECM stiffening acts as an upstream inflammatory trigger or a secondary inflammatory byproduct—and whether resultant matrix stiffness creates a self-amplifying mechanical feedback loop sustaining chronic lesions—remains to be resolved via longitudinal preclinical and human tissue studies. Longitudinal studies capturing early pre-lesional changes and *in vivo* temporal perturbation experiments are required to determine whether mechanical signals precede immunological signals.

Fibroblast subtype verification

The CD44hi papillary fibroblast subpopulation described is defined primarily by immunophenotyping. Whether it corresponds to an independently stable functional subtype at the single-cell transcriptomic level requires systematic validation through lineage tracing and spatial transcriptomics approaches [20]. And key functional data are currently derived from animal models. Whether DEJ mechanical measurements can be reproducibly obtained from human biopsy specimens and correlated with clinical disease activity indices (PASI) and biologic treatment response constitutes a critical gateway for translational advancement.

Confounding effects of age and sex

An additional underrecognized confounding variable across all current mechanochemical psoriasis research, including the landmark work of Jiang *et al.*, is the absence of stratification by biological age and sex. Psoriasis demonstrates consistent sex-based disparities in onset age, PASI severity trajectory, and biologic therapeutic response; concurrently, baseline dermal ECM stiffness, collagen cross-linking abundance, and fibroblast mechanosensory signaling sensitivity are profoundly modulated by age and sex steroid signaling. None of the cited preclinical murine psoriasis models or human skin biopsy cohorts control for age and sex as co-variates when measuring DEJ mechanical properties, LGALS9 expression, or downstream HMGB2-RRM2 activity. For translational mechanochemical therapeutic development, future human tissue studies must stratify patient samples by age and sex to define subgroup-specific ECM mechanical signatures, and all preclinical mechanobiology assays should incorporate age-matched male and female animal groups to avoid biased mechanistic conclusions and misaligned clinical trial design.

Therapeutic Paradigm Shift: From "Anti-Inflammatory" to "Anti-Inflammatory + Anti-Fibrotic" Combination Strategies

Existing biologic therapies for psoriasis, including anti-IL-17A/F and anti-IL-23p19 antibodies, primarily target soluble cytokines and demonstrate substantial efficacy, yet approximately 20%–30% of patients experience primary non-response or secondary treatment failure [7,8]. This suggests that suppressing chemical inflammatory signals alone may be insufficient to reverse established mechanical microenvironmental anomalies.

Therapeutic strategies targeting the LGALS9-CD44-HMGB2-RRM2 circuit offer distinct mechanistic advantages and can be approached:

Upstream chemical signal interception

LGALS9 neutralization and CD44-LGALS9 blocking strategies have yielded promising anti-inflammatory and anti-fibrotic preclinical results in human skin and systemic fibrotic disease models [18,10,34]. LGALS9-neutralizing antibodies or small-molecule CD44-LGALS9 binding antagonists could sever the pathological DC-to-fibroblast signal at its origin.

Matrix stiffness normalization

LOX inhibitors (e.g., BAPN), anti-fibrotic compounds (pirfenidone analogs), and hyaluronidase can soften already-stiffened ECM, fundamentally eliminating mechanical signal aberrations and restoring physical homeostasis of the skin microenvironment [26,32]. This class of strategies does not depend on systemic immunosuppression.

Selective integrin-FAK pathway intervention

Targeted inhibitors designed against integrin subtypes specific to papillary dermal fibroblasts could block mechanical signal transmission to HMGB2 with elevated tissue selectivity, potentially reducing systemic adverse effects [12,23].

Importantly, two major clinical constraints temper broad systemic anti-fibrotic intervention for psoriasis: first, robust dermal ECM stiffening and fibrosis are restricted exclusively to a subset of long-standing, refractory psoriatic plaques; mild or acute lesions exhibit minimal collagen cross-linking and DEJ mechanical aberrations, meaning anti-fibrotic mechanotherapies would only benefit a defined patient subgroup. Second, systemic administration of broad anti-fibrotic agents (oral pirfenidone, systemic LOX inhibitors) carries well-documented off-target toxicities including hepatic, pulmonary, and hematologic adverse effects—an unacceptable risk-benefit profile for a non-life-threatening inflammatory dermatosis.

To resolve this translational barrier, localized tissue-targeted mechanomodulatory modalities represent a far safer, more clinically actionable therapeutic framework, including three core approaches: (1) topical formulations of LGALS9/CD44 small-molecule antagonists applied directly to lesional skin to interrupt DC-fibroblast chemical signaling without systemic exposure; (2) intralesional injection of hyaluronidases or selective LOX inhibitors to soften stiffened DEJ ECM in isolated resistant plaques; (3) nanoparticle-encapsulated integrin-FAK inhibitors with dermal papillary fibroblast tropism for local mechanotransduction blockade. Combinatorial regimens would pair standard systemic anti-cytokine biologics with localized anti-fibrotic mechanotherapy for fibrotic refractory plaques, avoiding pan-systemic fibrosis suppression and minimizing whole-body adverse events.

It is noteworthy that researchers have employed nanoscale mechanical sensing patches to achieve real-time capture of local stiffness dynamics in the DEJ region of live murine psoriasis models, with concurrent spatiotemporal observation of HMGB2 nuclear translocation peaks in CD44+ fibroblasts [5,22]. This technical advance provides methodological foundations for clinical measurement of matrix mechanical status and outcome monitoring for the aforementioned novel therapeutic strategies.

Conclusion

These findings reshape our understanding of skin homeostatic imbalance, suggesting that the integrated regulation of mechanical and chemical signals constitutes the common pathological substrate of inflammatory dermatoses. Future therapeutic strategies may need to evolve from a singular "anti-inflammatory" paradigm to a combined "anti-inflammatory plus anti-fibrotic" approach, with

priority placed on localized lesion-targeted ECM modulators to avoid systemic toxicity. By simultaneously targeting the immune-mediated chemical signaling axis and the mechanotransduction-driven physical signaling axis, deep remodeling of the skin microenvironment may be achievable, offering patients with refractory inflammatory skin diseases more durable disease remission.

Future research priorities should focus on: (1) establishing quantitative correlations between matrix stiffness and disease activity indices in human skin biopsies with age and sex stratification; (2) initiating early-phase clinical trials targeting the LGALS9-CD44 axis or localized ECM-softening strategies; (3) systematically evaluating the universality of the HMGB2-RRM2 axis as a cross-disease biomarker and therapeutic target; (4) dissecting the hierarchical regulatory relationship between YAP/TAZ and HMGB2 under pathological matrix stiffening. The deep convergence of mechanobiology and cutaneous immunology represents the frontier of future inflammatory dermatosis research.

Acknowledgments

This work is supported by the National Natural Science Foundation of China (82003384), National Funded Postdoctoral Research Program (GZC20252830), China Postdoctoral General Support Program (2025M784536), Chongqing Special Funding for Postdoctoral Projects (2024CQBSHTB2013), China.

Conflict of Interest

The authors state no conflicts of interest.

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