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Nanochemical modulation of ECM-driven pseudo-resistance: convergent microenvironmental pathways in COVID-19 and cancer

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Extracellular matrix (ECM) remodeling is increasingly recognized as a central determinant of inflammation, fibrosis, and therapeutic response across chronic diseases. This Perspective examines how post-COVID-19 pulmonary fibrosis and stromal-driven resistance in solid tumors converge on a shared phenomenon, ECM-driven pseudo-resistance, an extrinsic and reversible microenvironmental state in which pathological matrix architecture, fibro-inflammatory signaling, and immune exclusion transiently limit therapeutic efficacy without conferring stable, mutation-driven cellular resistance. We highlight how nanochemical strategies, including ECM-penetrating and ECM-modulating nanohybrids, can dismantle these physical and signaling barriers by reprogramming matrix stiffness, mechanotransduction, and immune accessibility. By integrating evidence from virology, oncology, and materials science, this review proposes that targeting conserved ECM pathways through advanced nanochemistry offers a cross-disease therapeutic paradigm for overcoming pseudo-resistance in fibrotic and malignant pathologies.

Traditionally viewed as a structural scaffold, the extracellular matrix (ECM) is now understood as a dynamic biomechanical and biochemical regulator that directs cell fate, immune activity, tissue repair, and disease progression.[1–9] This expanded perspective reveals unexpected mechanistic overlap between post-COVID-19 pulmonary remodeling and stromal-driven therapeutic resistance in cancer, two conditions that appear unrelated but share a fundamental microenvironmental logic.[10]

Despite vast differences in origin and clinical course, COVID-19 and cancer, both exhibit a pathological transition in matrix architecture that allows cells to persist despite therapy. This ECM-driven pseudo-resistance arises from changes in stiffness, matrix cross-linking, dysregulated signaling, and immune-cell exclusion.[11–16] Viral injury and tumorigenesis alike generate ECM environments that promote survival, inflammation, and escape from therapeutic pressure.[17]

In oncology, resistance to therapy is traditionally categorized as intrinsic or acquired and is often attributed to genetic or epigenetic alterations within cancer cells.[18] However, an expanding body of evidence highlights a distinct, microenvironment-driven form of resistance that arises independently of stable genetic change.[18] This phenomenon is commonly referred to as stroma-mediated resistance, describing therapeutic failure driven by cancer-associated fibroblasts (CAFs), ECM remodeling, altered mechanotransduction, and immune exclusion within the tumor microenvironment.[19] In this Perspective, we adopt the term ECM-driven pseudo-resistance to delineate a related but conceptually broader and potentially reversible state, in which pathological ECM architecture and associated signaling networks transiently shield diseased cells from therapeutic pressure without conferring permanent cellular resistance. Unlike mutation-driven resistance, pseudo-resistance is extrinsic and context-dependent, and may be alleviated through microenvironmental reprogramming.[20] In physiological host defense and tissue repair, innate immune cells and stromal cells undergo a transient activation program that supports pathogen clearance and wound closure, followed by a resolution phase that restores homeostatic cell–matrix signaling. Failure of this resolution step can lock tissues into self-reinforcing fibro-inflammatory niches, where stromal remodeling and immune dysfunction persist even after the inciting trigger has diminished.[21]

Importantly, while stroma-mediated resistance is typically discussed within oncology, ECM-driven pseudo-resistance encompasses fibrotic and inflammatory pathologies beyond cancer, including post-viral tissue remodeling such as COVID-19–associated fibrosis, thereby providing a unifying framework across disease contexts.[22] This expanded framework further

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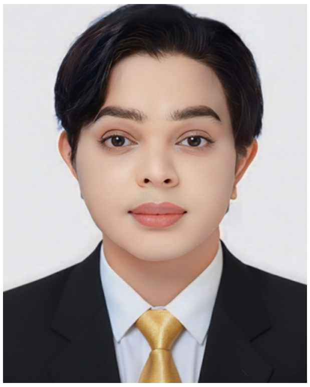
implies that acute inflammatory insults capable of reshaping tissue architecture may have consequences beyond the primary disease, influencing latent pathological states in distant or pre-existing lesions.

Notably, accumulating evidence suggests that severe respiratory viral infections, including SARS-CoV-2, can reawaken dormant tumor cells through inflammation-driven microenvironmental remodeling.[23–29] Systemic cytokine surges, neutrophil extracellular trap formation,[30] and virus-induced tissue injury collectively reshape the ECM and disrupt quiescent niches that normally restrain disseminated tumor cells. Recent studies have demonstrated that inflammatory remodeling of the lung stroma following viral infection can promote the outgrowth of previously dormant metastatic cells, highlighting a microenvironment-mediated mechanism rather than direct oncogenic transformation.[31] These observations parallel broader findings that infection-associated inflammation and ECM perturbation can accelerate metastatic awakening across multiple cancer models, reinforcing the concept that pathological ECM remodeling acts as a permissive trigger for tumor reactivation rather than a passive bystander.[31]

Patients with long COVID often respond poorly to corticosteroids, immunomodulators, and antifibrotic agents, even in the absence of viral persistence. Likewise, cancer patients may exhibit poor responses to chemotherapy, radiotherapy, or immunotherapy without classical resistance mutations. In both settings, the ECM itself; not the genome, creates therapeutic failure.[32]

This perspective reframes these parallel pathologies through the lens of nanochemical modulation, proposing that engineered nanomaterials capable of penetrating or altering pathological ECM represent a powerful strategy to overcome pseudo-resistance in both diseases (Fig. 1).



Sanoj Rejinold N

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Dr Jin-Ho Choy is a Chair Professor at Dankook University and the founding Director of the Intelligent Nanohybrid Materials Laboratory (INML). He is internationally recognized as a pioneer in layered double hydroxides (LDHs) and inorganic–organic nanohybrids, advancing these materials for applications in drug delivery, cancer therapy, and next-generation nanomedicine. His research encompasses nanomaterials synthesis, structural characterization, and functionalization, with broad impact across biomedicine, environmental science, and materials engineering. With more than 700 peer-reviewed publications, numerous international patents, and major honors from the Korean Chemical Society and the American Chemical Society, Dr Choy has secured extensive national and international research funding. He remains deeply committed to training and mentoring the next generation of scientists while driving innovations that continue to shape the future of nanoscience and medicinal chemistry.

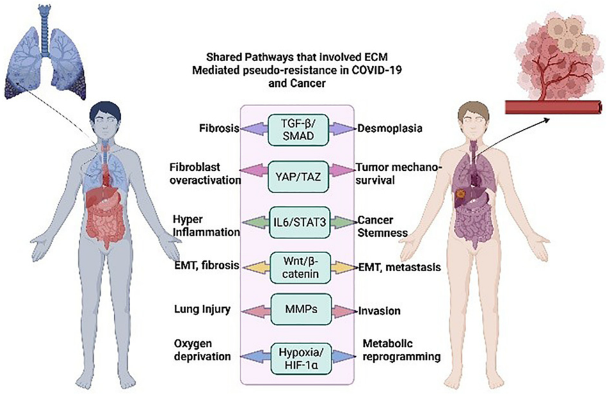

Fig. 1 Shared ECM-mediated pseudo-resistance mechanisms in COVID-19 and cancer. Pathological ECM remodeling in post-COVID fibrosis and in the tumor stroma converges on common signaling hubs—including TGF-β/SMAD-driven fibrosis, YAP/TAZ-regulated mechanosurvival, IL-6/STAT3-mediated hyperinflammation and stemness, Wnt/β-catenin-driven EMT, and MMP-dependent matrix turnover. These shared pathways generate stiff, immune-excluded, and therapy-insulating microenvironments that promote persistent dysfunction in both diseases (Figure was made using Biorender.com).

How reprogrammed ECM establishes pseudo-resistant states in COVID-19 and cancer

ECM remodeling is not merely an accumulation of fibrosis but a deep, system-wide reorganization of matrix proteins, proteoglycans, integrin networks, and mechanotransduction pathways.[33] In healthy tissue, the ECM operates as a dynamic regulator that constantly turns over, enabling immune surveillance, controlled inflammation, and regenerative balance. At the cellular level, this transition is accompanied by metabolic reprogramming that distinguishes transient repair from pathological persistence. Pro-inflammatory macrophage activation is commonly associated with a shift away from oxidative phosphorylation toward glycolysis, with the pentose phosphate pathway supporting NADPH-dependent oxidative burst and inflammatory effector functions.[34]

Conversely, stromal fibroblast activation programs engaged by profibrotic cues (*e.g.*, TGF-β) can increase metabolic demands for ECM production, where glutamine utilization and anaplerotic flux support collagen biosynthesis and matrix accumulation.[35] When resolution fails, these high-demand immunometabolic and fibrometabolic states can persist, reinforcing the ECM-remodeling and mechanotransduction circuits that sustain pseudo-resistant niches. But when this equilibrium is disrupted, whether by the inflammatory cascade triggered by SARS-CoV-2 infection or by the relentless remodeling driven by tumor growth, the matrix shifts into a pathological state. Its architecture stiffens, its biochemical gradients distort, and its signaling landscape becomes profoundly altered, trapping cells in survival-promoting, nonresponsive niches. What begins as an adaptive repair response transforms into a microenvironment that actively resists therapeutic interventions, creating the pseudo-resistant states that define both persistent post-COVID fibrosis and the desmoplastic stroma of solid tumors.[36]

ECM remodeling in COVID-19 fibrosis mirrors tumor desmoplasia

ECM remodeling in COVID-19–related fibrosis[37] bears a striking resemblance to the desmoplastic remodeling seen in solid tumors.[33] Following SARS-CoV-2 injury, fibroblasts become rapidly activated and engage profibrotic signaling programs such as TGF-β, Wnt, and SMAD, driving the overproduction of collagen, fibronectin, and matrix-crosslinking enzymes. The tissue gradually transforms into a dense, rigid, highly interconnected scaffold that limits the penetration of therapeutics, distorts immune-cell trafficking, and reinforces fibroblast activation through FAK, YAP/TAZ, and other mechanosensitive pathways. This pathological architecture mirrors the matrix produced by CAFs in aggressive tumors, where stiffness and signaling dysregulation collaborate to create treatment-resistant niches. Compounding this complexity, the inflammatory upheaval triggered by viral infection can destabilize previously dormant cancer cell reservoirs, potentially awakening quiescent tumor cells under conditions of microenvironmental stress.[38]

ECM-driven pseudo-resistance is reversible

Unlike mutation-driven resistance, which is genetically fixed, ECM-induced resistance arises from abnormal physical and biochemical remodeling of the matrix—and importantly, it is reversible. Strategies that soften, degrade, or reprogram the pathological ECM can restore a more permissive microenvironment. Re-establishing ECM homeostasis enables improved drug penetration, enhanced immune-cell infiltration, and renewed therapeutic responsiveness in tumors that were previously refractory. This reversibility underscores the ECM as a correctable and clinically actionable barrier.[39,40]

Although extensive preclinical studies demonstrate that ECM-driven pseudo-resistance can be reversed through matrix softening, enzymatic remodeling, or mechanotransduction blockade, translation to the clinic is inherently context-dependent.[41] The reversibility of pathological ECM states is influenced by factors such as disease stage, duration of fibrosis or desmoplasia, degree of collagen cross-linking, and stromal cellular heterogeneity. In advanced or long-standing disease, ECM remodeling may become partially stabilized through irreversible architectural changes, limiting the extent of functional normalization achievable with monotherapies. Clinical outcomes are therefore likely to depend on early intervention, combination strategies integrating ECM modulation with cytotoxic or immune therapies, and patient-specific matrix characteristics. Recognizing these constraints reframes ECM-driven pseudo-resistance as a ''*conditionally reversible*'' phenomenon, reinforcing the need for precision-guided and temporally optimized therapeutic approaches.

Clinical and translational efforts targeting ECM stiffening, mechanotransduction, and stromal inflammation demonstrate

Table 1 Clinical and translational evidence supporting conditional reversibility of ECM-driven pseudo-resistance

ECM target/strategy	Representative agent(s)	Clinical indication(s)	Clinical status/key findings	Implication for ECM reversibility	Key ref.
Collagen cross-linking (LOXL2)	Simtuzumab (anti-LOXL2 mAb)	IPF, liver fibrosis, pancreatic cancer	Phase II trials showed acceptable safety but limited efficacy as monotherapy in advanced disease	ECM stiffening can be biologically targeted, but late-stage fibrosis is only partially reversible	42
Hyaluronan-rich ECM depletion	PEGPH20 (pegylated hyaluronidase)	Pancreatic ductal adenocarcinoma	Improved drug penetration and PFS in HA-high tumors when combined with chemotherapy; safety concerns limited development	Functional ECM barriers can be reversed in selected patients	43
Mechanotransduction (FAK signaling)	Defactinib (VS-6063)	Mesothelioma, ovarian & pancreatic cancer	Combination trials showed stromal remodeling, enhanced immune infiltration, and acceptable safety	Downstream ECM signaling is reversible even if matrix structure persists	44
Fibro-inflammatory ECM programs (TGF-β)	Galunisertib (LY2157299)	HCC, pancreatic & solid tumors	Modest monotherapy activity; improved outcomes in combination regimens	ECM normalization is context-dependent and requires combination strategies	45
Stromal normalization (vascular + ECM)	Anti-VEGF–based combinations	Multiple solid tumors	Improved perfusion, immune infiltration, and therapy response	Partial ECM normalization can restore treatment sensitivity	46
Inflammation-driven ECM remodeling	Anti-IL-6/anti-TNF strategies (correlative)	Cancer, chronic inflammation	Reduced stromal inflammation correlates with improved therapy response	ECM reversibility is linked to inflammatory control	41

that pseudo-resistance can be functionally and conditionally reversed in selected disease contexts, although outcomes are highly stage- and strategy-dependent (Table 1).

Immune exclusion: a shared barrier in long COVID and cancer

In fibrotic post-COVID lungs, dense ECM remodeling physically restricts immune-cell entry into damaged tissue, perpetuating inflammation and impeding resolution.[47,48] Such spatial restriction is not only a trafficking problem but can also prolong inflammatory programming by maintaining a microenvironment that favors persistent pro-inflammatory immunometabolic states. Solid tumors create an analogous immune-excluded niche, where remodeled stroma blocks T-cell infiltration and blunts antitumor immunity.[49] The striking resemblance between these two conditions suggests that immune dysfunction in long COVID and immune resistance in cancer emerge from a common ECM-dependent origin.[23]

Nanochemical modulation: a convergence point for therapeutic innovation

Nanochemical modulation is emerging as a powerful meeting point where different therapeutic fields converge. What makes nanotechnology special is its ability to interact with the diseased ECM in ways that ordinary drugs simply cannot.[50] These nanoscale systems can move through stiffened, fibrotic tissue, influence the enzymes that tighten or distort the matrix, and interrupt the abnormal mechanical signals that keep cells locked in a pathological state.

Many kinds of nanomaterials can do this (Table 2 and Fig. 2a)). Some are designed to slip through dense ECM barriers.[37] Others can inhibit LOX or tune down TGF-β, softening the matrix or shifting it back toward a healthy architecture (Fig. 2b and c). To exemplify, a compelling demonstration of ECM-targeted chemistry comes from studies on lysyl oxidase–like 2 (LOXL2) inhibition in acute myeloid leukemia (AML). In the bone marrow niche, leukemic blasts bind tightly to collagen-rich ECM networks, forming highly protective anchorage points that shield them from chemotherapeutic stress. This physical and biochemical adhesion is a primary driver of pseudo-resistance, enabling AML cells to survive cytarabine and other frontline therapies even without acquiring genetic mutations. To break this protective barrier, researchers engineered bone-marrow–targeted yolk–shell nanoparticles carrying a hydrophilic LOXL2 inhibitor (LOXL2i). These LOXL2i-loaded DSS6 nanoparticles (LOXL2i DSS6-NPs) were constructed with a collagen I hydrogel yolk encased within a PEG-PLGA shell, achieving high drug-loading efficiency and selective homing to the bone marrow niche.

Once delivered, LOXL2 inhibition initiates a chemical dismantling of collagen cross-links—a central structural element that maintains ECM stiffness and cellular anchorage. By disrupting LOXL2 activity, the nanoparticles weaken collagen integrity, reduce ECM density, and block the contact-dependent adhesion of AML cells to their stromal microenvironment. This decoupling effect directly removes the pseudo-resistant state by preventing AML cells from entering ECM-mediated survival signaling. *In vitro*, LOXL2i DSS6-NPs significantly enhance nanoparticle penetration into stroma-rich spheroids and prevent leukemic cells from establishing collagen-dependent adhesion. *In vivo*, they remodel the collagen architecture and reduce ECM deposition within the bone marrow, effectively ‘‘softening’’ the leukemic niche. When combined with cytarabine, the targeted LOXL2 inhibition dramatically sensitizes AML cells to chemotherapy, leading to substantial reductions in leukemic burden in murine AML models. This synergy arises not from altering cancer cell genetics but from chemically reprogramming the microenvironment that shields them.

Overall, LOXL2i-loaded yolk–shell nanoparticles illustrate how precision ECM chemistry can successfully overcome pseudo-resistance. By breaking stromal adhesion, dismantling collagen cross-linking, and restoring drug accessibility, LOXL2 inhibition stands as a powerful example of how ECM-targeting

Table 2 Chemical & nanochemical modulation criteria for destroying ECM-driven pseudo-resistance in COVID-19 and cancer

Criterion	Biological rationale/ pseudo-resistance basis	Mechanistic goal	Representative mechanisms/ examples	Supporting evidence	Key limitations/translational constraints
1. Confirm ECM-driven resistance, not purely genetic	Requires validated ECM biomarkers; difficult to stratify patients clinically	Identify fibrosis/ desmoplasia as the *true* barrier	Increased collagen, fibronectin, TGF-β; restored drug response after ECM modulation	51	Requires validated ECM biomarkers; difficult to stratify patients clinically
2. Target ECM stiffening & collagen cross-linking	Limited efficacy in late-stage fibrosis; potential off-target connective tissue effects	Reduce LOX/LOXL2-mediated rigidity	LOXL2i yolk–shell nanoparticles soften bone-marrow ECM and re-sensitize AML	52	Limited efficacy in late-stage fibrosis; potential off-target connective tissue effects
3. Block integrin–FAK–YAP mechanotransduction	Systemic inhibition may affect normal tissue mechanobiology	Interrupt survival signals from stiff ECM	SDC4–integrin-αvβ1 axis; FAK inhibitors; reduced YAP/TAZ activation	53	Systemic inhibition may affect normal tissue mechanobiology
4. Reopen immune & drug access	Risk of excessive matrix degradation and vascular leakage	Restore T-cell infiltration and drug penetration	Collagenase nanocarriers; ECM-softening nanoparticles	54	Risk of excessive matrix degradation and vascular leakage
5. Normalize (not destroy) ECM architecture	Fine control required to avoid impaired wound healing	Restore physiological turnover & biomechanics	Controlled TGF-β/Wnt suppression; reduced excess collagen I/III	54	Fine control required to avoid impaired wound healing
6. Localize ECM modulation using targeted nanosystems	Target specificity varies with ECM heterogeneity	Avoid global toxicity, concentrate effects in fibrotic zones	Bone-marrow-targeted DSS6 NPs; CAF/Tumor-membrane-coated MOFs	55	Target specificity varies with ECM heterogeneity
7. Combine ECM modulation with frontline therapy	Combination toxicology and dosing schedules need optimization	Convert refractory lesions into therapy-responsive ones	LOXL2i + cytarabine; FAK inhibition + radiotherapy	52	Combination toxicology and dosing schedules need optimization
8. Prioritize cross-disease micro-environmental modulators	Long-term safety across indications must be established	Use agents active in fibrosis, inflammation, and cancer	Nano-niclosamide (NIC–MgO–HPMC) modulates Wnt/STAT3/TGF-β	56	Long-term safety across indications must be established
9. Ensure reversibility & biomarker monitoring	Lack of standardized clinical ECM biomarkers	Maintain organ integrity while softening ECM	Use stiffness, ECM fragments, IL-6, collagen turnover markers	57	Lack of standardized clinical ECM biomarkers
10. Evaluate effects on metastatic/pre-metastatic niches	Timing of intervention critical; late intervention less effective	Prevent fibrosis-induced metastatic escape	ECM remodeling linked to dormancy awakening	58	Timing of intervention critical; late intervention less effective

nanochemistry transforms therapeutic outcomes in otherwise refractory malignancies.[59]

Therapeutic failure in AML is increasingly recognized as a consequence of ECM remodeling within the bone marrow niche rather than solely intrinsic genetic resistance. In murine AML models, leukemic progression is accompanied by excessive collagen deposition, enhanced fibronectin organization, and LOXL2-mediated collagen cross-linking, resulting in a mechanically stiffened microenvironment that limits drug efficacy. AML cells residing within this fibrotic niche display marked resistance to cytarabine despite unchanged intrinsic drug sensitivity, indicating a microenvironment-driven pseudo-resistant state. Disruption of pathological ECM architecture restores chemosensitivity, directly implicating stromal remodeling as a dominant determinant of therapeutic response.[51]

Certain nanosystems target integrins to break the cycle of FAK/YAP activation, while others calm down the chronic fibro-inflammatory loops that maintain disease. A striking demonstration of how the ECM itself drives pseudo-resistance comes from recent work on syndecan-4 (SDC4), a key mediator of ECM–cell mechanotransduction in pulmonary fibrosis. Using decellularized lung ECM as a physiologically faithful substrate, researchers showed that fibrotic ECM actively amplifies fibroblast activation through an SDC4-dependent upregulation of integrin-αvβ1. This signaling loop enhances integrin expression, promotes FAK/AKT phosphorylation, and sustains TGF-β1 production—precisely the pathways that stiffen tissue, perpetuate fibrosis, and recreate tumor-like desmoplasia in the injured lung. Disrupting SDC4, either genetically, with blocking antibodies, or *via* the rationally designed SDC487–131-derived peptide CS-9, collapses this mechanotransduction axis, inhibits fibroblast activation, and prevents fibrotic ECM from reinforcing its own pathological state. Mechanistically, the SDC4–integrin-$\alpha_v\beta_1$ complex emerges as a central amplifier of ECM-driven inflammation and remodeling, revealing a fundamental principle that echoes across cancer, viral fibrosis, and chronic inflammatory disease: the ECM is not a bystander but an active instructive signal that locks tissues into pseudo-resistant states.[53]

Using decellularized fibrotic lung ECM as a physiologically faithful substrate, controlled suppression of TGF-β and Wnt signaling was shown to normalize, rather than ablate, pathological matrix architecture by reducing excess collagen I/III deposition and restoring balanced ECM turnover. This approach preserved essential biomechanical support while reversing aberrant stiffness and fibroblast hyperactivation, thereby re-establishing physiological cell–matrix signaling without inducing tissue fragility. Importantly, ECM normalization reinstated immune accessibility and therapeutic diffusion while maintaining structural integrity, demonstrating that selective reprogramming of matrix signaling, rather than wholesale ECM degradation, is sufficient to dismantle pseudo-resistant states driven by fibrosis and desmoplasia.[54]

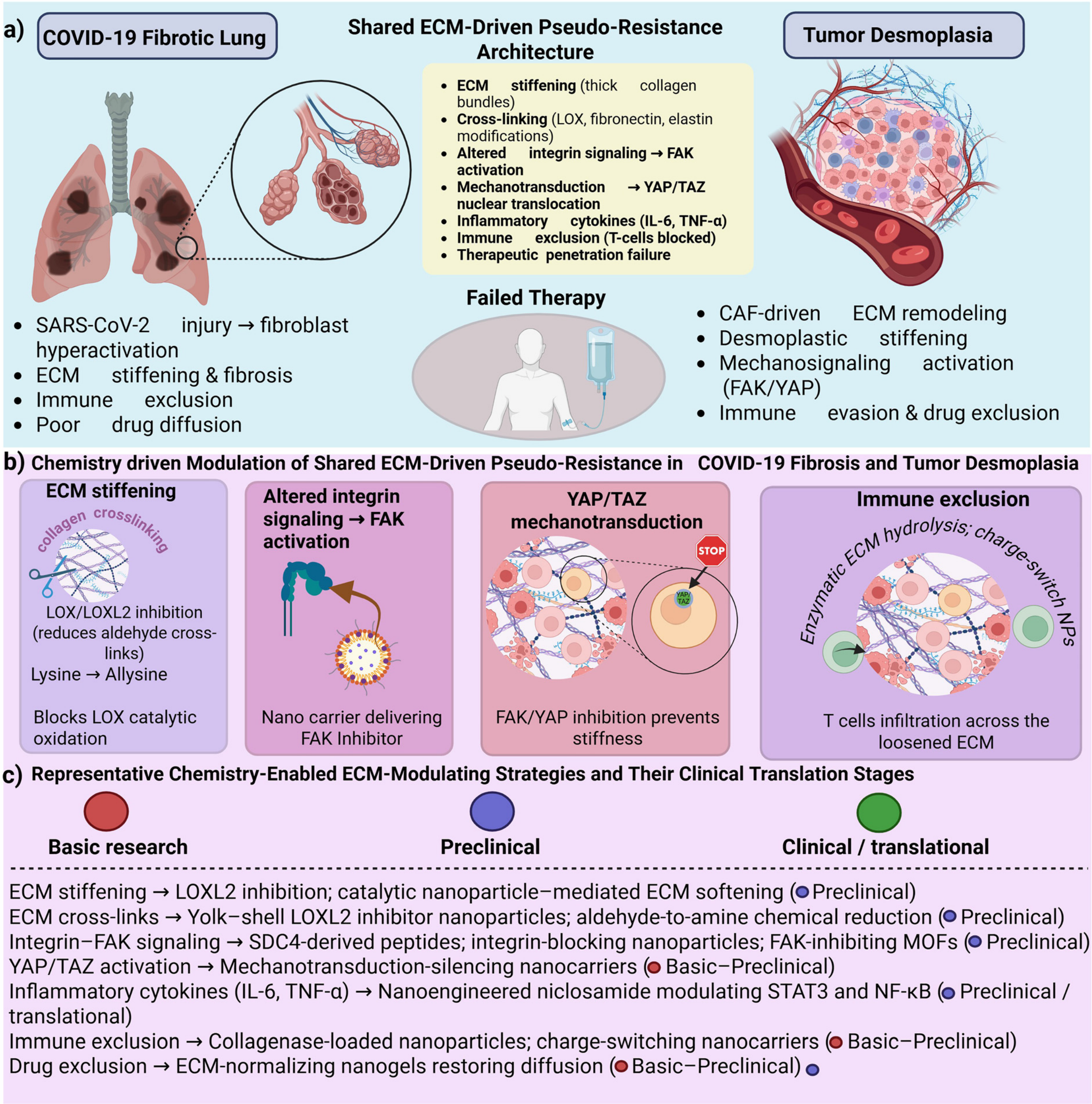

Fig. 2 Shared ECM-driven pseudo-resistance and its nanochemical disruption in COVID-19 fibrosis and cancer. (a) Schematic comparison of COVID-19–associated fibrotic lung remodeling and tumor desmoplasia, highlighting their shared extracellular matrix (ECM)–driven pseudo-resistant architecture. In both settings, fibroblast or cancer-associated fibroblast (CAF) activation induces excessive ECM stiffening, collagen cross-linking, altered integrin–FAK signaling, YAP/TAZ mechanotransduction, inflammatory cytokine production, immune exclusion, and impaired drug penetration, culminating in therapeutic failure; (b) chemical and nanochemical modulation of shared ECM-driven pseudo-resistance pathways. Targeted nanochemical strategies disrupt key pathological features, including LOX/LOXL2-mediated collagen cross-linking, integrin–FAK signaling, YAP/TAZ mechanotransduction, inflammatory cytokine signaling, immune exclusion, and diffusion barriers, thereby loosening the fibrotic matrix and restoring tissue accessibility; (c) summary of representative chemistry-enabled ECM-modulating interventions annotated by their current stage of clinical translation, distinguishing basic research, preclinical development, and clinical/translational evaluation. LOXL2 inhibition and catalytic nanoparticles soften the ECM by preventing or destabilizing collagen cross-links; SDC4-derived peptides, integrin-blocking nanoparticles, and FAK-inhibiting nanoplatforms suppress aberrant mechanosignaling; nanoengineered niclosamide attenuates IL-6/STAT3 and NF-κB–driven inflammation; collagenase-loaded and charge-switching nanoparticles restore immune infiltration; and ECM-normalizing nanogels recover effective drug diffusion. Together, these approaches illustrate how nanochemical modulation can reprogram pseudo-resistant niches into therapy-responsive microenvironments across COVID-19 fibrosis and cancer. (Figure created using BioRender.com.).

This fibroblast-centric regulatory logic is not unique to pulmonary fibrosis; it mirrors the same stromal activation programs that dominate the tumor microenvironment. Just as SDC4–integrin signaling in the fibrotic lung creates a self-reinforcing pathological niche, CAFs deploy analogous integrin–FAK–YAP circuits to stiffen the matrix, elevate inflammatory cues, and construct a protective stromal architecture around malignant cells. In both settings, the ECM becomes an active generator of resistance, teaching the surrounding stroma to shield rather than support tissue, and setting the stage for therapeutic failure.

In a recent study, researchers addressed a major limitation of radiation therapy (RT) for advanced cervical cancer: although RT remains the cornerstone of treatment, local recurrence is frequent because tumors gradually acquire microenvironmental radioresistance, rather than resistance driven solely by DNA mutations. Among all stromal components, CAFs exert the greatest influence on this failure. Their intrinsic resistance to ionizing radiation, along with radiation-induced activation, establishes a fortified stromal niche that shields tumor cells, accelerates repair, and drives relapse. This CAF-reinforced TME represents a textbook example of ECM-driven pseudo-resistance, where the biology of the stroma; not oncogenic genetics, governs therapeutic escape.

To dismantle this stromal barrier, investigators developed a biomimetic metal–organic framework (MOF) nanoplatform designed for dual-target radiosensitization. The system combines two synergistic components:

(1) IN10018, a potent FAK inhibitor that disrupts CAF mechanotransduction, reduces fibroblast infiltration, and weakens the ECM architecture responsible for radioresistant phenotypes.

(2) Bismuth (Bi), a high-Z element embedded within a ZIF-8 framework to enhance radiation absorption, thereby amplifying RT-induced DNA damage and ROS generation in tumor cells.

The resulting IN10018–Bi-loaded ZIF-8 nanoparticles (IZB NPs) were then cloaked with hybrid membranes derived from CAFs and cervical cancer cells, enabling dual-targeting precision.

- CAF-mimetic surface cues promote homing to stromal fibroblasts, where IN10018 suppresses CAF radioresistance at its mechanochemical root.
- Tumor-cell-derived markers facilitate direct accumulation within cancer cells, enhancing radiation sensitization.

In the acidic conditions of the TME, the MOF disassembles, triggering controlled release of IN10018 to inhibit FAK activation and reduce stromal density. Concurrently, Bismuth intensifies local radiation deposition through enhanced photoelectric interactions, boosting ROS production and DNA damage.

Together, targeted ECM modulation and stromal signaling disruption weaken the protective extracellular matrix (ECM) shield that underlies CAF-mediated pseudo-resistance and limits radiotherapy efficacy in cervical cancer. Inhibition of LOXL2-driven collagen cross-linking softens the desmoplastic matrix and reduces stromal stiffness, thereby diminishing mechanotransduction-dependent survival signaling and improving radiosensitivity within both cancer and stromal compartments (Fig. 2b and c).[55] Concurrent suppression of integrin–FAK signaling and YAP/TAZ activation further disrupts force-dependent transcriptional programs that sustain radioresistant phenotypes under stiffened ECM conditions.[56] ECM loosening also restores immune and therapeutic access by alleviating physical exclusion of cytotoxic lymphocytes and enhancing intratumoral diffusion of radiosensitizing agents (Fig. 2b).[57] In parallel, nanoengineered modulators targeting inflammatory cytokine circuits, including IL-6 and TNF-α, attenuate CAF-driven fibro-inflammatory feedback loops that otherwise promote stromal survival and post-irradiation recurrence.[58]

Collectively, these coordinated nanochemical functions dismantle microenvironmental resistance rather than directly targeting cancer cell genetics, thereby converting a radio-refractory tumor niche into a therapy-responsive state and providing a rational strategy to enhance radiotherapy outcomes in cervical cancer (Fig. 2).

Although these examples arise from oncology, the underlying principles extend far beyond cancer (Fig. 2a). What emerges from LOXL2 inhibition in leukemia and CAF-targeted radiosensitization in cervical cancer is a deeper realization: pseudo-resistance is not a tumor-specific phenomenon, but a shared ECM-mediated survival strategy seen across diverse diseases. The same biochemical motifs—collagen over-crosslinking, LOX/LOXL2 hyperactivity, TGF-β–driven fibroblast activation, aberrant mechanotransduction, and stalled tissue remodeling—also define the persistent fibrosis and immune dysfunction observed in long COVID and other chronic viral injuries. In COVID-19, for instance, viral inflammation recruits fibroblasts, amplifies TGF-β and SMAD signaling, stiffens the ECM, and rebuilds lung tissue into a desmoplasia-like architecture that mirrors solid tumors. This stiffened matrix restricts drug penetration, traps immune cells at the periphery, perpetuates YAP/FAK activation, and establishes a chronic inflammatory loop indistinguishable from the stromal barriers that protect refractory cancers. Thus, whether the context is chemotherapy, radiotherapy, or antiviral treatment, the ECM acts as a central gatekeeper that determines therapeutic access, cellular responsiveness, and long-term disease persistence. By viewing COVID fibrosis and cancer through the same ECM framework, nanochemical modulation becomes a unifying strategy capable of breaking pseudo-resistant states across multiple pathologies.

These insights position nanochemical systems as more than isolated solutions for individual cancers—they reveal a unifying therapeutic logic across diseases. Although clinical nanomedicine interventions for COVID-19–associated pulmonary fibrosis remain limited, accumulating preclinical and translational studies demonstrate the feasibility of nanotechnology-based modulation of fibrotic ECM remodeling in viral lung injury. There are also multifunctional hybrids that remodel the ECM and deliver therapeutics at the same time. Nano-engineered niclosamide (NIC–MgO–HPMC) illustrates this convergence beautifully.[60,61]

Unlike enzyme-targeting ECM modulators, niclosamide operates through a distinct physicochemical mechanism based on membrane-associated acid–base and proton-transfer chemistry. Niclosamide belongs to the salicylanilide class and fulfills the canonical chemical requirements of mitochondrial uncouplers, namely weak acidity, pronounced hydrophobicity, and electron-withdrawing substitution. The phenolic OH group of salicylanilides undergoes reversible acid dissociation, and the presence of both the phenolic OH and the anilide NH is a critical structural requirement for uncoupling activity. Quantitative structure–activity analysis indicates that these functionalities contribute to increased lipophilicity and efficient proton translocation across the mitochondrial membrane, consistent with a protonophoric uncoupling mechanism.[62] Quantitative structure–activity relationship analyses of salicylanilide derivatives have shown that the presence of electron-withdrawing substituents, particularly at the phenolic ring, is associated with enhanced uncoupling activity, reflecting favorable acid dissociation properties and increased lipophilicity required for protonophoric function.[63] By uncoupling mitochondrial proton translocation from ATP synthesis, niclosamide induces a state of cellular energy limitation that has been shown to suppress activation and profibrogenic functions of ECM-producing cells.[64] Experimental studies demonstrate that mitochondrial uncoupling or modulation of oxidative phosphorylation reduces ATP availability, attenuates TGF-β–dependent signaling, and inhibits the activation, proliferation, and collagen-producing phenotype of fibrogenic cells such as hepatic stellate cells and myofibroblasts.[65] Consequently, when nano-engineered for effective penetration into dense and fibrotic matrices, niclosamide is expected to destabilize ECM-driven pseudo-resistant states not by chemically degrading the extracellular matrix itself, but by impairing the energy-dependent cellular programs required to actively maintain pathological microenvironmental architecture.

By penetrating stiff, fibrotic tissue, dampening fibro-inflammatory signaling, and restoring cellular responsiveness, NIC nanohybrids resolve the very microenvironmental barriers that sustain pseudo-resistance. What is striking is that these effects manifest not only in tumors but also in virally injured organs, including the fibrotic lung in long COVID.[61] In other words, the same ECM-softening, crosslink-modulating, and mechanotransduction-resetting principles that sensitize cancers to therapy can also reverse post-viral fibrosis and chronic immune dysfunction.

Altogether, these capabilities point to a broader truth: nanochemical modulation is inherently cross-disease. It offers a unified strategy wherever pathological ECM emerges as the dominant obstacle whether in long COVID fibrosis, immune exhaustion syndromes, dense and desmoplastic solid tumors, or even the stromal reactivation events that trigger metastatic awakening.[66] Nanochemistry's power lies in its ability to reach, reprogram, and normalize the ECM itself, transforming tissues that were once refractory into environments that can finally respond to therapy.

From a clinical translation perspective, however, the impact of nanochemical ECM modulation must be evaluated beyond preclinical efficacy. While many ECM-targeting nanoplatforms remain at *in vitro* or *in vivo* stages (Fig. 2c), several related strategies—such as LOX/LOXL2 inhibition, mechanotransduction blockade, and nanoformulated anti-inflammatory agents have progressed into early clinical or advanced translational evaluation, demonstrating that stromal and matrix remodeling can be safely manipulated in humans. Clinical feasibility will ultimately depend on long-term biocompatibility, controlled biodistribution within fibrotic tissues, scalable manufacturing, and compatibility with existing standards of care. Notably, nanochemical systems built from clinically validated materials, employing oral or inhalable delivery routes, and designed to sensitize tissues rather than replace frontline therapies appear particularly well positioned for near-term translation. These considerations underscore nanochemical ECM modulation as an emerging but realistic clinical strategy, while highlighting the importance of stage-aware development and rigorous validation.

Challenges and translational considerations in ECM-targeting nanochemistry

Despite their promise, ECM-targeting nanomaterials face several challenges that must be addressed to enable clinical translation. Safety and long-term biocompatibility remain key concerns, as prolonged retention of inorganic or non-degradable nanomaterials within fibrotic tissues may lead to off-target toxicity or chronic inflammation. Targeting efficiency is further complicated by inter- and intra-patient heterogeneity in ECM composition, stiffness, and vascular accessibility, which can limit uniform nanoparticle penetration and distribution. In addition, large-scale manufacturing, batch-to-batch reproducibility, and regulatory standardization remain non-trivial hurdles for complex nanochemical systems. Emerging strategies—including biomimetic surface functionalization, disease-responsive or biodegradable nanoplatforms, localized delivery approaches, and the use of clinically validated materials, are being actively explored to overcome these limitations.

Importantly, emerging ECM-modulating nanoplatforms are beginning to demonstrate translational feasibility when developed under rigorous safety-by-design principles. In this context, CP-COV03 (NIC–MgO–HPMC); a nanoengineered niclosamide drug designed to overcome solubility, stability, and bioavailability limitations, has undergone systematic long-term biocompatibility evaluation. By integrating MgO nanoparticles with hydroxypropyl methylcellulose (HPMC), the nanohybrid achieves enhanced pharmacological performance while maintaining a safety profile compatible with repeated dosing.[67]

In prior *in vivo* assessments extending over 13 weeks, toxicological evaluation focused on hepatic, renal, and hematologic systems, with clinical observations, serum biochemistry, and hematological parameters showing no treatment-limiting abnormalities at clinically relevant doses. Histopathological analysis of major organs revealed no evidence of tissue damage or structural alteration, supporting the long-term tolerability of the nanohybrid. While extended toxicology under diverse clinical scenarios remains necessary, these findings establish an important foundational safety benchmark for chronic or repeated administration of nanoengineered niclosamide systems.[67]

Collectively, the demonstrated tolerability of CP-COV03 supports its potential applicability across disease contexts that require sustained or repeated dosing, including persistent viral infections such as long COVID, preparedness against future pandemic threats, and oncology indications, where ECM modulation may be deployed in combination with standard therapies.[67]

Concluding perspectives and distinct contributions

This feature review article introduces ECM-driven pseudo-resistance as a unifying and conceptually distinct framework that extends beyond traditional, cancer-centric views of therapy resistance. While existing literature has extensively described stroma-mediated resistance within oncology, this review advances the field by explicitly positioning pathological ECM remodeling as a reversible, cross-disease microenvironmental state that operates across cancer, post-viral fibrosis, and chronic inflammatory conditions.

A key contribution of this work is the integration of virology, oncology, and nanochemistry, highlighting mechanistic parallels between COVID-19–associated fibrotic remodeling and tumor desmoplasia that are rarely addressed together in existing reviews. By synthesizing evidence across these traditionally separate disciplines, this review reframes therapeutic failure as an ecosystem-level phenomenon, driven by ECM architecture, mechanotransduction, and immune exclusion rather than irreversible genetic change alone.

In contrast to prior reviews that focus primarily on individual signaling pathways or nanomaterial classes, this article provides a mechanism-anchored, translationally informed roadmap for ECM modulation. The delineation of core regulatory criteria, associated translational limitations, and clinical-stage annotations offers practical guidance for evaluating which ECM-targeting strategies are most likely to succeed in real-world settings. Importantly, by incorporating long-term safety considerations and clinical evidence where available, this review emphasizes conditional reversibility and translational realism over conceptual optimism.

Together, these contributions position ECM-targeting nanochemistry not as a niche strategy confined to oncology, but as a broad, disease-agnostic therapeutic paradigm. By explicitly linking microenvironmental biology to clinical feasibility, this review aims to guide future research toward rational, stage-aware, and safety-conscious ECM-modulating interventions capable of overcoming pseudo-resistance across diverse pathological contexts.

Conflicts of interest

Authors have no conflicts of interest to declare.

Data availability

No new experimental or computational data were generated as part of this review. All data discussed in this article are derived from previously published studies, which are appropriately cited in the reference list.

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