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Nanoscale opportunities in extracellular matrix mimicry

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We present an overview of the composition, function, energetics, and dynamics of extracellular matrix and its relation to nanoscale structures and phenomena. These concepts are then related to the development of synthetic and biosynthetic materials that aim to mimic the extracellular matrix for regenerative medicine and tissue engineering technologies. Notable successes and advancements towards the goal of biomimicry are outlined, while remaining challenges and knowledge gaps towards that goal are highlighted. Finally, we frame the remaining challenges in the field in terms of nanoscience-related research opportunities that if solved, might prove to be transformative steps forward in the discipline.

Introduction

Living systems work by dynamically moving materials and energy across a breadth of length scales, with the time scales of those dynamics being similarly broad. In tissues, this exchange mainly happens through the extracellular matrix (ECM),[1–4] a dynamic tissue scaffold that spans a broad hierarchy of time, energy, and distance. The ECM combines mechanical properties, spatial organization, energy storage and release, and ongoing remodeling to guide how cells behave and how tissues function.[3,5] Because of this central role, researchers have spent considerable effort trying to reproduce parts of the ECM in synthetic tissue scaffolds and biomaterials.[4–7] The long-term goal of that work is to regenerate complex tissues by combining engineered materials with the body's natural healing and developmental processes.[6,7] In this Focus Article, we will frame that goal in terms of ECM structure, dynamics, and energetics, with special attention to the nanoscale features that strongly influence its behavior. We

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conclude by offering perspectives on promising future directions, with a particular focus to nanoscale structures and processes.

The ECM

Structure

The ECM mainly consists of structural proteins (*i.e.*, collagens and elastin) that provide mechanical integrity, glycoproteins (fibronectin, laminins, *etc.*) that are responsible for further organizing the ECM architecture, and proteoglycans and GAGs (HA, aggrecan, *etc.*) – protein cores decorated with long carbohydrate chains, which are responsible for hydration, compressibility, and molecular signaling (Fig. 1).[6] Collagens (ranging from types I-XIV) are the dominant fibrous proteins in the ECM and account for roughly one-quarter to one-half of the total ECM protein content.[2,6,8–10] The fibers in these networks range from 50–500 nm in diameter, with pore sizes from ~10 nm to several microns and collagen orientations varying from random to highly aligned.[11–14] This structural hierarchy imparts complex mechanical properties to collagen[13,15] and controls how cells sense and respond to it, for example through integrin clustering and signaling.[1,16–18] Collagen is not just a passive support of cellular function, as it actively responds to forces from cells, typically responding to the formation and action of cellular focal adhesions.[15,19–22] These cell-induced stresses align the fibers into tracks that extend tens of microns, with fibers stiffening[23–27] the local environment to act as guidance cues for processes like durotaxis and collective cell migration.[15,28–30] During normal development, such alignment shapes tissues (*e.g.*, tendon formation),[31–34] while in indications like fibrosis and cancer, long-term contraction by cells produces dense, aligned matrices that encourage invasive cell behavior.[3,14,20,35–40]

Another layer of complexity in native ECM is its ligand diversity and co-presentation. Cells are not exposed to a single adhesion motif but rather to a composite microenvironment that integrates integrin-binding sequences (*e.g.*, RGD, PHSRN, GFOGER), glycosaminoglycan sulfation patterns, and growth factor–binding domains.[6,16,17,41–44] These motifs are often displayed in a mechanically and spatially regulated fashion; some remain cryptic until revealed by force unfolding or proteolytic cleavage.[18,45,46] Alongside collagen, glycosaminoglycans such as hyaluronan and chondroitin sulfate also help tissues retain water, creating swelling pressure that resists compression in cartilage and intervertebral discs.[13,47,48] Porosity is another important nanoscale feature of the ECM Fiber density and organization. Densely packed collagen fibrils (as in tendon) yield low porosity, while loose connective tissues (like dermis) exhibit high porosity. Hydrophilic components like glycosaminoglycans (*e.g.*, hyaluronan) swell in water, expanding pore space and increasing effective porosity, while enzymatic degradation or deposition of new ECM alters porosity dynamically. Overall, ECM pores have dimensions ranging from ~6 nm in cartilage to greater than 1 μm in loose connective tissue. Here, the term pore size is used in the transport sense: an effective

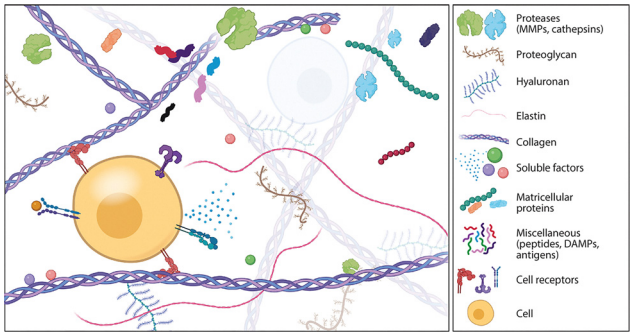

Fig. 1 Schematic depiction of the composition, organization, and function of the extracellular matrix. From Marjan *et al.*, *Annu. Rev. Biomed. Eng.*, 2025, **27**, 185, used under CC-BY 4.0 license.[6]

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steric or hydraulic mesh size is typically estimated from tracer diffusion or permeability measurements such as FRAP/FCS, partitioning, or multi-particle tracking, and supported by ultrastructural imaging. In cartilage, dense aggrecan-GAG assemblies restrict solute motion to an effective mesh on the order of a few nanometers, often reported ~3–6 nm depending on hydration or compaction, whereas in loose connective tissues fiber spacing and percolated void space can reach micron scales. Importantly, these values are tissue-, age-, and disease-dependent; for example, proteoglycan depletion, like in degeneration and osteoarthritis, generally increases permeability mesh size, while collagen accumulation and crosslinking, such as in fibrosis or tumors, can reduce effective pore space and increase tortuosity.[1,2,30,49–51] These pores control how growth factors and cytokines diffuse through the ECM, establishing gradients that guide cell migration and tissue development. This spatial organization of ECM is essential for guiding cell behavior and supporting tissue-specific function. *In vivo*, the ECM is anisotropic and compartmentalized, with well-defined microdomains that differ in fiber alignment, pore size, stiffness, and ligand presentation.[2,3,30] Examples include the stratified ECM of the basement membrane, the stiffness gradient at the osteochondral interface, or the aligned collagen bundles in tendon and muscle.[9,31,42,52–54] These structural features influence everything from cell polarity and orientation to mechanotransduction and lineage specification.

Thus, the nanoscale organization of ECM components plays a vital role in shaping how cells interpret and respond to their environment. For example, when cell receptors interact with their ligands in the extracellular matrix, the spacing of ECM-based binding sites can have a profound influence on cellular function.[6,29,42] Proteins such as collagen, fibronectin, and laminin assemble into highly ordered nanostructures with precise periodicities and geometries. Collagen type I fibrils exhibit a characteristic ~67 nm D-banding pattern, reflecting the staggered alignment of tropocollagen triple helices (Fig. 2).[8,55] For some fibrillar ECM architectures, nanoscale periodicities can place adhesion motifs in the tens-of-nanometers regime. Nanopatterning studies suggest integrin clustering and focal adhesion maturation are strongly supported when adhesive ligands are spaced within ~50–70 nm; however, the "optimal" spacing is not universal and depends on the ECM protein, assembly, as well as integrin subtype, ligand identity, and local mechanics.[1–3] Beyond the molecular and nanoscale signals, the ECM also shows major structural differences at the tissue level. Skeletal tissues vary widely in stiffness and porosity: cortical bone is dense and low in porosity, making it ideal for load bearing, while trabecular bone is much more porous, supporting fluid flow and energy absorption.[9,38,40,56–60] Tendons are built from highly aligned collagen fibers that give them strength in one direction,[11,32,47] whereas cartilage has a more random collagen network combined with water-retaining proteoglycans,[31,59,61–64] allowing it to resist compression from many directions. These spatial differences in structure and mechanics not only enable specialized functions but also create local gradients in adhesion and stiffness. Aligned fibers allow mechanical forces to travel over long distances, so that cells can sense and respond to forces generated by their neighbors. This long-range mechano-transmission helps coordinate collective cell behaviors during development, wound healing, and cancer invasion, linking events at the molecular and nanoscale to tissue-level organization and function.[18,21,27,56,65,66]

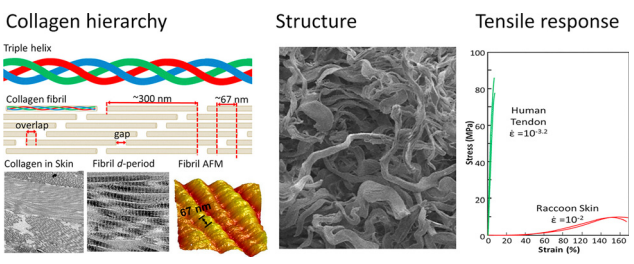

Fig. 2 Hierarchical structure of collagen and the relationship between its organization and mechanical response. Reprinted from *J. Mech. Behav. Biomed. Mater.*, **52**, V. R. Sherman, *et al.*, The materials science of collagen, Pages 22–50, Copyright (2015), with permission from Elsevier.[55]

Mechanics

As described above, the ECM has variable properties depending on where it is in the body and how it is organized. These properties are adapted to the specific function of each tissue, while disruptions in the ECM can contribute to various pathologies. For example, brain ECM is very soft (compressive modulus ~100 Pa)[22,67–69] but becomes stiffer as special structures called perineuronal nets form during growth,[3,68,69] which affects how neural stem cells behave.[22] In tendons, the ECM is made up of tightly packed, organized collagen fibers that provide uniaxial strength, with stiffness in the range of hundreds of megapascals.[11,32,34,47,70] In contrast, cartilage is built to resist compression with a combination of stiff collagen and water-binding macromolecules.[31,59,61–64,71] Tumors often cause the ECM to harden due to excessive collagen deposition, which promotes cancer spread and makes treatments less effective due to diffusion barriers at the tumor periphery.[6,14,49,72–76]

ECM is a viscoelastic material, with characteristics of both solids and liquids.[67,77–80] It can stretch or deform over time under pressure (a behavior called creep) and can gradually relax and dissipate stress when held under steady force. Additionally, ECM displays hysteresis following repeated loading and unloading cycles, like a spring that unfolds and dissipates some energy following repeated deformation.[12,77,81] These material properties can be seen in the wide range of energy dissipation responses observed in different tissues, where biological function connects directly to the time dependent mechanics (Fig. 3). On the nanoscale, this hysteresis arises from the way individual collagen fibers absorb energy when stretched and through the formation of subsequent irreversible modifications to fiber structure, or "memory" of the deformation.[8,12,14,26] Thus, fibrous networks composed of collagen and fibrin exhibit mechanical behaviors that change with stress, allowing tissues to dynamically absorb and release energy depending on the mechanical demands of their environment. A particular manifestation of this phenomenon is known as strain stiffening, where tissues remain

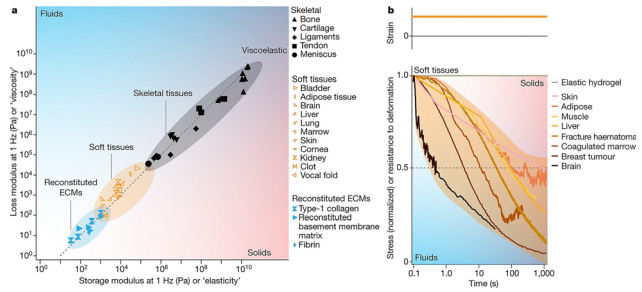

Fig. 3 Complex viscoelasticity (a) and stress dissipation rates (b) across a range of tissue types. Reprinted with permission from O. Chaudhuri, *et al.*, Effects of extracellular matrix viscoelasticity on cellular behaviour, *Nature*, **584**, p. 535, 2020, Springer Nature.[77]

compliant during low levels of strain but rapidly increase their stiffness under higher strain to prevent damage.[23–27,82] Thus, during normal movement or under potentially damaging stresses, the ECM can buffer forces through mechanisms like fiber alignment, crosslink rearrangement, and hysteretic deformation. These dynamic responses depend on both entropic and enthalpic contributions, creating an energetic environment that is constantly evolving in response to internal and external mechanical cues.

Another vital property of the ECM is its toughness, or resistance to structural failure.[14,55,77] This toughness comes from the internal forces associated with protein fibril assembly and the ability of fibers to slide and move hierarchically, which helps absorb energy during stress and prevents sudden failure. For example, in bone, sacrificial bonds within collagen fibers can break temporarily, revealing extra "hidden length" in the fibers, which spreads out the energy of a fracture and prevents catastrophic failure of the bone.[60] This is a particularly excellent example of how forces are transmitted through the hierarchy of biological structures, and how the structural and energetic properties across that hierarchy serve to support the overall function of the material. At the tissue level, mechanical heterogeneity is not only functional but may also serve as a diagnostic marker. For example, the mechanical properties of breast tissues show that malignant tumors exhibit bimodal stiffness distributions, in contrast to the unimodal profiles of healthy tissue.[35] These data suggest that mechanical patterning within the ECM reflects, and may also influence, pathological states. Similarly, the measurement of micrometer-scale domains in histological slices of multiple organs illustrated that collagen-rich regions were stiffer than collagen-poor zones, directly linking biochemical and mechanical heterogeneity in real tissue.[9]

Energetics

As suggested above, the mechanical properties of ECM are closely tied to how energy flows and dissipates within it, which is essential for tissue development, repair, and function. At the microscopic and molecular level, collagen fibers in the ECM are coated with molecules called proteoglycans, which attract water and create hydrated layers that help dissipate energy when the fibers slide against each other.[1–3,47,83] Larger deformations of the ECM cause fibers to bend and temporary bonds to break, allowing mechanical energy to be absorbed and rearranged without causing permanent damage. Cellular activity within the ECM also benefits from this hierarchical distribution of energy. For example, cells use ATP to generate mechanical forces by contracting their cytoskeleton *via* myosin II activity.[27,45,72,84–86] These forces pull on the ECM through focal adhesions that feed back to stiffen and align the ECM, which can influence processes like cell metabolism, signaling and adhesion.[87] Interestingly, stiff ECM increases cellular energy production in the form of glycolysis and mitochondrial activity,[21] while a softer ECM decreases the activity of those pathways and promotes a more energy-efficient state called oxidative phosphorylation.[18] Mechanistically, these metabolic shifts arise from stiffness-dependent mechanotransduction through integrin:focal adhesion complexes, which activate signaling cascades such as focal adhesion kinase (FAK) and Src family kinases, as well as RhoA/ROCK-mediated cytoskeletal tension and downstream YAP/TAZ nuclear signaling.[88–90] Increased cytoskeletal tension and YAP/TAZ activation on stiffer matrices upregulate glucose transporter expression, enhance glycolytic enzyme activity, and engage PI3K–Akt–mTOR pathways that support mitochondrial biogenesis and metabolic flux.[91–93] In contrast, softer matrices reduce mechanotransductive force transmission, suppress YAP/TAZ signaling, and favor a lower-energy-demand state with enhanced reliance on oxidative phosphorylation.[94–96] This two-way connection ensures that cells generate sufficient energy to meet their mechanical demands, effectively linking cellular metabolism with the physical properties of the ECM.

Cellular energetic impact on the ECM is also seen in how enzymatic activity serves to continually remodel the environment. Key enzymes such as matrix metalloproteinases (MMPs) break down components of the ECM such as collagen and elastin,[49,97,98] while LOX enzymes crosslink collagen to make the fibers stronger.[97,99] This structural balance is especially important in processes like wound healing, where the ECM transitions from a provisional structure to a more permanent one. However, when this balance is disrupted, it can lead to pathological tissue development such as that seen in fibrosis or cancer. In fibrotic tissues, LOX creates abnormal crosslinks that increase stiffness and reduce function.[36–40,97,99] In cancerous tissues, MMPs help tumor cells invade by breaking ECM barriers while LOX strengthens tumor environments, which then resist pharmacological treatments.[20,73,76,99–101] These ECM dynamics occur over a range of timescales, further illustrating the hierarchical nature of biological tissues. For example, stress relaxation occurs over a time period of seconds to hours,[25,66,102–104] facilitating a dynamic interplay between cells and their environment. Small-scale changes like bond breaking or fiber sliding happen in milliseconds, while large-scale tissue remodeling or turnover takes weeks, months, or years.[1,36,38] These processes involve both reversible changes, such as temporary deformation, and irreversible modifications, such as those seen in enzymatic remodeling.

Together, the complex energetic, structural, temporal, and mechanical properties of ECM clearly illustrate the significant challenges associated with ECM mimicry. On their own,

mimicking any of these factors in a synthetic or biosynthetic architecture represents a massive experimental challenge. The biochemical complexity of tissue remodeling might be mimicked through the controlled release of MMP or LOX enzymes, or through the introduction of enzyme-sensitive units, but the other remodeling processes associated with mechanical deformation or stress dissipation in the matrix might not be represented in such a structure. Similarly, mimicry of ECM's viscoelastic or self-healing properties might be feasible over a narrow range of length scales (and hence time- and energy-scales) but recapitulating that across the entire scale and hierarchy of an organ is synthetically challenging. Below, we describe some notable examples of nanoscale ECM mimicry that have attempted to bridge these gaps. Finally, we will present some future opportunities where nanoscale engineering might push the field even closer to true ECM-mimetic materials.

Nano-engineering of ECM mimics

Given the vast biophysical, structural, and dynamic features of ECM, the opportunities for mimicry using synthetic- or biocomposite-based approaches are similarly broad. Some ECM-mimetic designs include naturally derived scaffolds, such as decellularized ECM,[5,58,105] fibrin,[106] and hyaluronic acid,[102,107,108] to capitalize on bioactivity, while synthetic, polymer hydrogel-based systems allow for high reproducibility and tunable mechanical strength.[42,82,104,109] Nanofibrous scaffolds, often assembled through electrospinning or colloidal self-assembly, provide a useful method to replicate fibrillar ECM structures and to direct cell spreading and alignment,[31,33,110–115] while microporous annealed particles (MAP) and other granular hydrogels supply architectures with high porosity and permissive remodeling capabilities on the micron scale.[50,116–118] Furthermore, reversible and stimuli-sensitive chemistries within hydrogels have been developed to precisely control cell signaling through ligand exchange, introduce dynamic mechanics, exhibit specific degradability, and more.[6,17,42,119,120] The use of biosynthetic materials is appealing because they harness the bioactivity of natural components while providing mechanical durability and tunability that comes from an engineered system. Whereas this Focus Article is not intended to be a comprehensive review of the literature, we will offer some examples of nanostructured materials that thoughtfully mimic key ECM structures or properties, allowing us to illustrate the design rules used, outcomes generated, and limitations experienced.

Explicit scaffold requirements related to strength, toughness, porosity, and cellular cues are dictated by the tissue to be replicated. In the case of bone engineering, for example, Zhang, *et al.* integrated magnesium-doped nano-hydroxyapatite (Mg-nHA) into polyvinyl alcohol/chitosan (PVA/CS) composites to create a rationally designed bone scaffold.[121] PVA/CS provides a 3D, non-toxic, and porous environment for bone tissue engineering, while Mg-nHA is effective in promoting osteogenic differentiation of bone marrow-derived mesenchymal stem cells (BMSCs). In this approach, PVA improves the strength and flexibility of the material to overcome chitosan's brittleness while retaining its degradability. Nanostructured HA is osteoconductive but lacks strength, which is resolved by magnesium doping that reduces fracture propensity. The chosen components leverage advantages from one another to create a suitable environment for the proliferation and differentiation of BMSCs. Here, the function of the nanoscale particles is both structural and bioactive, thus permitting the material to achieve outcomes that bulk polymers could not alone.

Molecular/nano-engineering of biological components has also been successful. In one example, recombinant human type III collagen (hCOLIII) was layered with hyaluronic acid (HA) to form an ECM mimetic coating on a polylactic acid (PLA) abdominal aorta stent to enhance endothelization and decrease neointimal hyperplasia in a rabbit model (Fig. 4).[122] Here, researchers used recombinant technology to remove platelet-binding motifs normally found on collagen (to avoid thrombosis) while retaining its other cell-instructive attributes. Control over ligand presentation at the nanoscale allowed the researchers to design an ECM mimetic coating that decreased the amount of scar tissue and overall failure rate of aortic stents. In another molecular engineering example, Zhao *et al.* argued that a frequent concern in

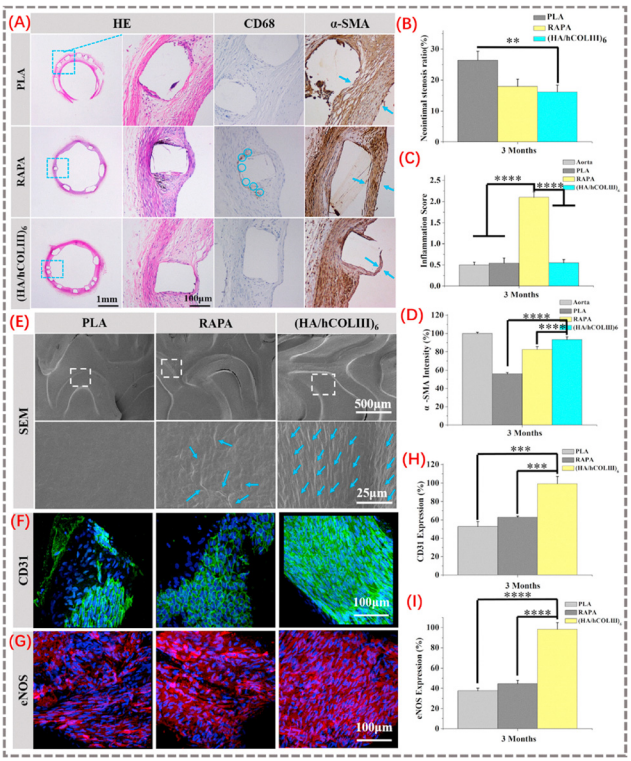

Fig. 4 Inflammatory and wound healing responses to implanted abdominal aortic stents modified with nanostructured, ECM-mimetic coatings in a rabbit model. Healing outcomes are significantly improved as a result of the nanostructured coating. Reprinted from *Biomaterials*, **276**, Yang, L. *et al.*, A tailored extracellular matrix (ECM) - Mimetic coating for cardiovascular stents by stepwise assembly of hyaluronic acid and recombinant human type III collagen, p. 121055, Copyright (2021), with permission from Elsevier.[122]

microenvironments for tissue regeneration is oxidative stress. They developed a self-assembling fibril glycopeptide hydrogel (Nap-FFGRGD@FU) functionalized with Arg-Gly-Asp (RGD) peptides and the polysaccharide fucoidan to enhance the deposition of cartilage.[63] In this structure, fucoidan directly scavenges reactive oxygen species (ROS) and activates the NRF2 pathway, regulating the redox equilibrium during cell proliferation and thereby modulating inflammatory responses.

Biosynthetic materials have also made significant contributions to the field of skin regeneration and wound healing. For example, glucomannan hydrogels coupled with CAP ($(DOPA)_4$-G_4-GRGDS) peptides boast high-water content, porosity, tunability, and antioxidant properties that have been shown to promote the healing of pressure ulcers in rats.[110] This material employs a straightforward preparation process to facilitate the polarization of macrophages from an M1 to an M2 phenotype while reducing ROS, thereby restoring tissue architecture without the use of additional growth factors. In another study, the group used a hyaluronic acid and chitosan hydrogel (OHA-CMC) encapsulating modified curcumin (CNP) and epidermal growth factor (EGF) to address the prolonged inflammation and oxidative stress that prevents diabetic wounds from healing.[107] By leveraging the occlusive nature of the hydrogels, the antioxidant and anti-inflammatory properties of curcumin, and the cell proliferation and migration capabilities of EGF, the group was able to successfully close wounds with significantly decreased inflammation while regenerating blood vessels and hair follicles of diabetic mice. Fibrous networks have also been developed using biologically sourced, renewable nanomaterials such as cellulose nanofibers.[112] The intrinsic anisotropy of those nanoparticles permits their assembly into bioinspired nanostructured fibrous networks that mimic the structure and mechanics of collagenous materials. Such materials have been proposed for applications such as organoid development and stem cell delivery, where explicit tailoring of the mechanical environment holds the potential for directing cellular fate or the maturation and subsequent of specific organs or tissues.

ECM mimetic approaches that focus on submicron structures closely mimicking the organization found in native ECM have begun to emerge. Roosa *et al.* developed flowable, porous fibrin nanoparticles (FBNs) fabricated through probe sonication and coupled them with keratinocyte growth factor to address issues in wound healing.[114] When combined with fibrinogen in the absence of exogenous thrombin, this unique approach to wound closure successfully stops bleeding while promoting angiogenesis and HUVEC cell sprouting. Additionally, tuning the concentration of FBNs allows for considerable control over porosity as compared to current dense fibrin sealants, thereby enabling highly tunable polymerization kinetics. This group has also functionalized a natural fibrin scaffold with colloidal FBNs that have a wide range of mechanical properties dependent on concentration, thereby enabling the development of a new class of surgical sealants.[115] Importantly, the researchers demonstrated that the FBN nanoparticles greatly improved the structure and function of fibroblast and HUVEC networks and subsequent healing response as compared to those developing in high-density fibrin glues currently in clinical use (Fig. 5).

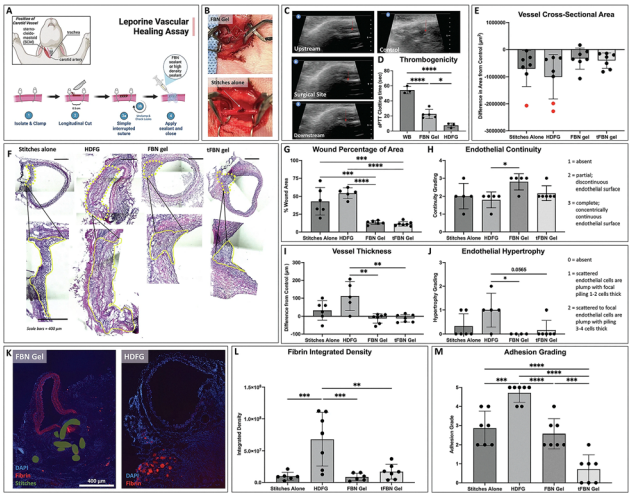

Fig. 5 Fibrin nanoparticle-based gels form the basis of a biomimetic surgical sealant in a rabbit vascular healing model. Similar healing outcomes are observed as compared to traditional surgical sutures while the new formulation outperforms high density fibrin glue surgical sealants across a range of measures and outcomes. From Moiseiwitsch *et al.*, *Commun. Eng.*, 2025, **4**, used under CC BY-NC-ND 4.0 license.[115]

Network porosity and crowding are attributes of ECM that have been an area of active focus of the biomaterials field. A particularly dynamic area of research relates to the microporous annealed particles (MAP) platform.[116,118] MAP gels and scaffolds typically employ hydrogel microparticles over a size range from tens to hundreds of microns that are then packed into a granular material to create a bulk scaffold. In this fashion, one can create a highly processable biomaterial wherein gel composition is controlled at the many-micron scale while enabling porosity much larger than the size of invading cells, thereby maximizing mass transport and cellular invasion rates.[108] When using this approach, the Segura group demonstrated that large pore sizes ($\sim$130 μm microgels) within scaffolds supported mature collagen regeneration, fewer inflammatory macrophages, and a higher epidermis:dermis ratio, more closely mimicking the structure of normal human skin compared to other microgel sizes and controls.[50] Building on this work, highly porous MAP scaffolds were combined with heparin-norbornene nanoparticles covalently bound to stromal cell-derived factor 1- alpha (SDF-1α) to regrow and repair stroke-damaged vasculature.[123] In this approach, the MAP scaffolds provided an interconnected microporous structure for cell infiltration and mechanical strength, while the SDF-1 nanoparticles led to improved neuronal progenitor cell (NPC) infiltration and functional vessel formation (Fig. 6). It is important to note that modifying the chemistry and porosity of the MAP gels alone was not enough to induce NPC migration, but that the combination of porous MAP particles and heparin nanoparticles produced excellent outcomes, thereby demonstrating the utility of designing materials with a hierarchical structure. The MAP scaffolds provided a microscopic structure and porosity to support the material mechanics and mass transport, while the nanoparticles enabled local cellular interactions and molecular control.

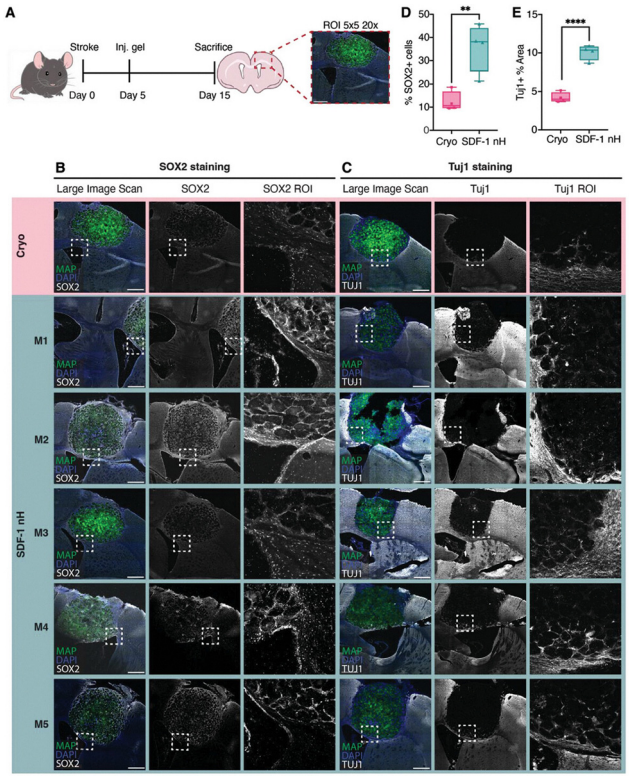

Fig. 6 Impact of SDF-1 nanoparticle-laden MAP cryo scaffolds on cell recruitment in a murine stroke model. Reprinted from *Adv. Healthcare Mater.*, **13**, Wilson, K. L. *et al.*, SDF-1 Bound Heparin Nanoparticles Recruit Progenitor Cells for Their Differentiation and Promotion of Angiogenesis after Stroke, p. 2302081, Copyright (2024), with permission from Wiley.[123]

Hierarchical material platforms have begun to extend this concept of integration to the nanoscale regime. For example, recent work from our laboratory introduced hierarchical collagen:microgel composites that recapitulate some aspects of nanoscale crowding, dynamic mechanical feedback, and multiscale porosity within a single material platform.[124] In that study, nanoscale microgel crowding promoted collagen fibrillogenesis; enabled cell invasion through the crowded material *via* yield-stress behavior; supported fibroblast proliferation and matrix remodeling; and increased the mechanical stiffness of the bulk material by many orders of magnitude over that of the native collagen gel – outcomes that are difficult to achieve simultaneously in conventional hydrogel systems. These results provide a proof-of-concept that nanoscale control over crowding, mechanics, and dynamics can be integrated into scalable biomaterials and leveraged to improve regenerative performance, supporting the feasibility of the opportunities outlined below. Other approaches to tailored scaffolds have focused on reversible and/or stimuli-sensitive chemistries within materials for precise control over mechanics, biochemical cues, and other directors of cell fate. A dynamic approach equips a material with on-demand remodeling capabilities to reproduce the responsive nature of the ECM. For example, Rosales *et al.* developed hyaluronic acid substrates permissive to softening by photodegradation and stiffening by photo-crosslinking over a range of moduli found in various ECM tissues.[125]

Interdisciplinary approaches

An emerging opportunity to advance ECM mimicry is the use of nanoscale-engineered matrices in organ-on-a-chip models (OoC). OoC models provide an environment with controlled shear, flow, and oxygen gradients and are beneficial in terms of control over independent variables, combining material types, and reducing the burden on animal testing. Common applications of ECM mimetics and OoC models are drug testing, biosensing, and tissue engineering.[126,127] Zamprogno *et al.* developed a lung-on-a-chip to recapitulate the thin air-blood barrier. The device was made by drop-casting a collagen–elastin ECM mimetic solution onto a gold mesh to support alveoli arrays, one side of which is in contact with air and the other with culture media. The nanoscale organization and optimal mechanics of the air–liquid interface enabled by this design permit cells to be cultured for weeks at a time while closely mimicking the lung parenchyma and respiration.[128] Similarly, Monteiro *et al.* engineered a perfused tumor-on-a-chip system utilizing an ECM-like matrix consisting of a human-derived methacryloyl platelet lysate (PLMA)-based hydrogels where co-cultured human bone marrow MSCs and tumor cell lines resided. The authors found that this hydrogel environment, rich in ECM proteins and growth factors, provided protection from cellular shear forces while maintaining interstitial fluid flow, thereby modulating tumor growth and invasion.[129]

Beyond just experimental methods to mimic the native ECM's structure and function at the nanoscale, artificial intelligence (AI) and machine learning (ML) are being used at rapidly evolving rates to assist in the prediction of new and improved materials.[130,131] Recent work has developed an easy-to-use ML tool to design ECM mimetic hydrogels with tailored rheological properties using click chemistry crosslinking to alter gelatin- and HA-based hydrogel stiffnesses. This method links nanostructure compositions and interactions to macro-scale outputs to achieve more scalable, reproducible, and efficient means to advance biomaterials.[132] We caution, however, that the sub-field of ECM mimicry currently lacks the diversity and robustness of training data required for ML implementation and compositional prediction. This in and of itself represents a significant challenge and opportunity in biomaterials development.

This article presents just a few examples where researchers have employed clever nanoscale design to introduce ECM biomimicry into scaffolds, which are summarized in Table 1. We stress that this is an extremely active area of research that has produced hundreds of examples of nanoscale ECM design, the full accounting of which is outside the scope of this Focus Article. The curious reader is encouraged to explore the literature more deeply to appreciate the range of approaches that have been taken.

Untapped opportunities

As illustrated above, tremendous progress has been made in the development of new cell and tissue scaffolds through reductionist mimicry of ECM. Highly engineered materials

Table 1 Examples of ECM-mimetic materials that enable hierarchical tissue regeneration across diverse applications

Material class/aim	Design description	Design outcomes	Ref.
Biosynthetic bone scaffold	Magnesium-doped nano-hydroxyapatite in polyvinyl alcohol/chitosan composites	Promotes osteogenic differentiation of BMSCs through mechanical integrity	121
Molecularly engineered ECM stent coating	Recombinant human type III collagen layered with hyaluronic acid	Reduces scar tissue and overall failure of aortic stents	122
Self-assembling glycopeptide hydrogel	Self-assembling fibril glycopeptide hydrogel functionalized with RGD and fucoidan	Hydrogel increases collagen deposition while fucoidan maintains redox equilibrium	63
Biosynthetic wound healing hydrogels	Glucomannan hydrogels with CAP peptides	Nanoscale signaling and porosity facilitates the polarization of macrophages and tissue regeneration	110
Biosynthetic wound healing hydrogels	HA and chitosan hydrogel encapsulating modified curcumin and epidermal growth factor	Decreases prolonged inflammation from diabetic wounds and increases wound healing rate	107
Nanoparticle fibrin systems	Porous fibrin-based nanoparticles coupled with keratinocyte growth factor	Efficiently stops bleeding and induces angiogenesis	114
Nanoparticle fibrin systems	Fibrin scaffold with colloidal FBNs	Improves function of HUVECs and fibroblasts as well as healing outcomes compared to dense fibrin glues	115
Microporous annealed particle (MAP) scaffolds	PEG-VS microgels crosslinked with MMP-sensitive peptides, RGD, K and Q peptides, factor XIII, and thrombin	Supports mature collagen regeneration, fewer inflammatory macrophages, and a preferred epidermis:dermis ratio	50
Microporous annealed particle (MAP) scaffolds	HA-norbornene microgels annealed into MAP scaffolds using tetrazine-PEG linkers combined with heparin–norbornene nanoparticles covalently bound to SDF-1α	MAP hydrogel scaffold provides a site for cell infiltration while SDF-1 improves neural progenitor cell recruitment and vessel formation	123
Dynamic phototunable hydrogel	HA modified with *o*-nitrobenzyl acrylates, methacrylates, and RGD, photocrosslinked with DTT	Hydrogels change their mechanics through photodegradation and photopolymerization	125
Lung-on-a-chip	Drop-casted collagen–elastin solution on a gold mesh to support alveoli arrays	Mimics the lung parenchyma and respiration through an air–liquid interface	129
Tumor-on-a-chip	Human-derived methacryloyl platelet lysate-based hydrogels with co-cultured human bone marrow MSCs and tumor cell lines	Supports tumor growth by providing an environment rich in ECM proteins and protection from shear forces while under flow	130
Machine learning (ML) to design ECM hydrogels	Gelatin and HA-based hydrogels altered with click chemistry	An easy-to-use ML platform predicts composition of materials needed to obtain desired rheological properties	133

have addressed a range of ECM properties: porosities that enable rapid cell invasion and nutrient transport; tunable mechanical and viscoelastic properties that connect to cellular mechanosensing; biochemical cues at the appropriate ligand densities and length scales to elicit strong cellular responses; and degradation properties that are dependent upon the native enzymatic processes to mimic tissue remodeling. However, combining all these factors, and other emergent properties, into a single materials platform has yet to be demonstrated. Furthermore, there are additional features of biological tissues that have seen far less attention in the field of tissue scaffold design.

Indeed, a simple bibliometric analysis of papers published since 2015 suggests a continued lack of focus on nanoscale features of ECM mimics and the hierarchical nature of ECM (Fig. 7). When analyzing papers describing ECM (bio)mimicry, we find that ~8400 papers were published on those topics over that period, with papers explicitly discussing 'micro' (~50%) or 'nano' (~30%) related topics representing a constant percentage of those papers year over year. However, when we consider terms that explicitly refer to the hierarchical nature of ECM (*e.g.*, 'hierarch*' as a keyword) or a phenomenon such as crowding, which is dependent upon nanoscale organization (*e.g.*, 'crowd*' as a keyword), the number of published papers decreases significantly, with less than 10 papers being published per year that relate to crowding. Even using the term 'nanoscale', which more precisely relates to a material's features, properties, and organization, results in only ~20–35 ECM mimicry papers per year, even though the term 'nanoscale' was used ~114 000 times overall in the literature during the same period. Clearly, despite increasing interest in ECM mimicry, the consideration of how nanoscale organization impacts the structure and properties of those materials remains a small percentage of the field's efforts without evidence of any trends towards increased activity. Given this current context, we describe some of the areas viewed as opportunities for significant impact on the development of ECM-mimetic, bio-integrative scaffolds as they pertain to nanoscale features, properties, and organization.

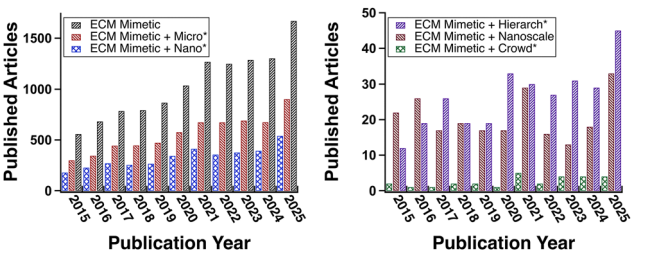

Fig. 7 Bibliometric analysis of publication trends in ECM mimicry since 2015. Articles explicitly describing micro- or nanoscopic objects or features consistently represent ~50% (micro) and ~30% (nano) of the total over that period (Left). When considering keywords explicitly related to nanoscopic organization or properties such as hierarchy or crowding, the total number of publications is a small fraction of the total, with no obvious time-dependent trends in term usage.

Crowding

Macromolecular and nanoscale crowding is a critical, yet often overlooked, feature of the ECM.[133,134] *In vivo*, tissues contain a dense milieu of macromolecules (typically 20–80 mg mL^{-1}), which significantly reduces the available free volume and alters fundamental physical behaviors such as molecular diffusion, protein folding, self-assembly, and intermolecular interactions. This dense environment creates what is known as the excluded volume effect, where crowding agents limit the space available for biomolecular motion and interactions, leading to accelerated reaction kinetics and altered thermodynamics of matrix assembly.[133–135] In contrast, most standard *in vitro* environments used in 2D or 3D culture are comparatively dilute, often containing ~4–16 mg mL^{-1} of macromolecules. This discrepancy results in a substantial gap between the physical microenvironment that cells experience *in vitro versus in vivo*, potentially contributing to poor matrix deposition and limited physiological relevance of tissue models. ECM-mimetic scaffolds often inherit this deficiency, lacking the crowded, viscous or viscoelastic microenvironment found in native tissues.

Several studies have demonstrated the powerful effect of mimicking crowding *in vitro*, and these findings have important implications for translational applications in tissue engineering. For example, Lareu *et al.* reported a 20- to 30-fold increase in collagen deposition when inert, charged macromolecular crowders such as dextran or Ficoll were added to cell cultures, highlighting how crowding can dramatically accelerate matrix assembly.[136] More recent work has continued to validate and extend this concept, illustrating the dramatic influence of crowding on matrix deposition by a mouse fibroblasts (Fig. 8). Polymer-based crowders enhance ECM protein maturation, improve phenotypic fidelity, and shorten the time needed for scaffold remodeling, which are key advantages in systems where timely matrix production is a limiting factor.[137–139] This is particularly significant because one of the persistent bottlenecks in clinical tissue engineering is the prolonged culture period required for cells to synthesize and organize their own ECM before a construct becomes suitable for implantation or analysis. In many cases, this maturation phase takes weeks to months, limiting clinical feasibility and increasing cost, labor, and variability.[5,140,141] The challenge is especially acute in time-sensitive therapeutic contexts such as wound healing, cardiac patching, or the generation of autologous grafts. Incorporating nanoscale crowding elements into synthetic scaffolds offers a promising strategy to address this barrier.[140] Crowded microenvironments promote protein–protein interactions, increase the local concentration of secreted matrix components, and accelerate fibrillogenesis, leading to faster and more robust ECM deposition.[136] Critically, these effects go beyond reducing culture time: by facilitating rapid matrix assembly, cells reach stable phenotypic states sooner, leading to more predictable and consistent scaffold performance.[141] Additionally, crowding-induced organization often yields ECM architectures that more closely resemble native tissue in terms of fiber density, alignment, and mechanical properties - factors known to influence graft function and integration post-implantation.[137,139] Taken together, these insights establish macromolecular crowding not only as a useful experimental tool, but as a nanoscale design principle for improving the efficiency, fidelity, and translatability of engineered ECM systems.

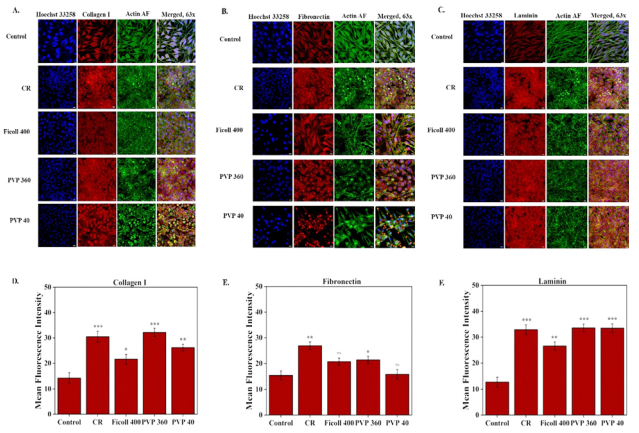

Fig. 8 Impact of macromolecular crowding on deposition of extracellular matrix components. Matrix organization and deposition density depends upon the identity of the crowding agent. Reprinted with permission from B. Guchhait, M. Kumari, S. Kaity and S. Roy, *ACS Applied Bio Mater.*, 2025, **8**, 6701. Copyright 2025 American Chemical Society.[142]

Current ECM mimics, however, often fail to reproduce crowding across a full-size spectrum. Most approaches either rely on small polymeric crowders (*e.g.*, Ficoll or polyethylene glycol)[134,137–139,141,143] or on extremely large-scale particulate inclusions (*e.g.*, MAP scaffolds),[50,69,108,123,144] leaving an underexplored regime of intermediate-scale nanoscale crowders. This mid-range crowding may better match the native ECM's dynamic balance between porosity, confinement, and mechanical responsiveness depending on the biological context, tissue type, or cellular phenotype. This is because the optimal level of crowding and confinement is inherently context-specific, varying with the structural and functional demands of different physiological environments. For example, recent work using multiple particle tracking in brain ECM revealed that pore size and local crowding vary across brain regions and disease states,[68] demonstrating that even within a single organ system, ECM architecture is highly heterogeneous and dynamically regulated. Materials that offer modular control over nanoscale architecture could more faithfully mimic these variables within *in vivo* testbeds.

Mechanics, energetics, and dynamics

The time- and stress-dependent properties of ECM are vital components of tissue healing, maturation, and toughness. However, conventional hydrogels such as those composed of poly(ethylene glycol)-diacrylate (PEGDA), tetra arm PEG gels, polyacrylamide, and alginate, for instance, are typically characterized by a single, fixed Young's modulus or storage modulus and are linearly elastic, providing a fixed stiffness regardless of applied stress, thereby lacking the ability to dissipate or store mechanical energy in an ECM-mimetic fashion.[42] Processes such as cell spreading, migration, or fate specification that are sensitive to mechanical feedback

are therefore less likely to mimic native tissue processes when placed in static mechanical environments.[82] In contrast, hydrogels with engineered viscoelastic properties, such as stress relaxation and frequency-dependent responses, have been shown to significantly enhance cell spreading, migration, and lineage specification, particularly in stem cells.[71,82,104]

Emerging studies further underscore the importance of designing scaffolds that incorporate this energetic nuance. For example, hydrogels engineered with stress-stiffening properties have been shown to better regulate mechanosensitive pathways like YAP/TAZ signaling and cytoskeletal remodeling, compared to their linear-elastic counterparts.[66] Work from the Anseth group has shown that hydrogels crosslinked with covalent adaptable networks permit reversible bond exchange, tuning viscoelasticity to match cellular timescales, providing a more dynamic environment that mimics the natural ECM.[52,119] Similarly, Heilshorn and colleagues showed that protein-engineered hydrogels with tunable viscoelasticity, designed to mimic the neural ECM, can more precisely regulate neural stem cell fate and morphogenesis.[58,67] These findings clearly illustrate that the dynamic and energetic landscape created by nonlinear mechanics is not just a passive feature of ECM, but an active regulator of cell behavior.

Spatial organization

Whereas the mechanics, energetics, biochemistry, and dynamics of ECM are vital, interrelated features, the influence of spatial organization on those factors is a true opportunity in nanoengineered matrices. The absence of spatial heterogeneity can disrupt key cell–matrix interactions, for example.[6,18] In durotaxis, cells detect and migrate along stiffness gradients, revealing how even subtle spatial variations in matrix mechanics can guide cellular behavior.[28,145] Isenberg *et al.* showed that vascular smooth muscle cells (VSMCs) cultured on polyacrylamide hydrogels with linear stiffness gradients preferentially migrated toward stiffer regions, and that both the magnitude of the gradient and the absolute stiffness modulated this behavior (Fig. 9).[145] Hartman *et al.* highlighted that durotactic responses are also ligand-dependent, as VSMCs exhibited durotaxis on fibronectin-coated gradients but not on laminin-coated ones, illustrating the interplay between mechanical heterogeneity and biochemical context in directing cell migration.[28] These findings underscore that not only are mechanical gradients cell-instructive, but their effects are modulated by ECM composition, making spatial heterogeneity in both stiffness and ligand presentation essential for guiding cell behavior.

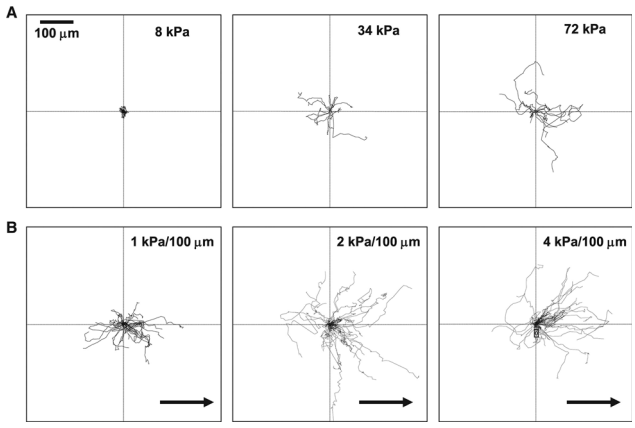

Fig. 9 Vascular smooth muscle cell migration. On uniform gels (A), migration is non-directional, while stiffness gradients (B) induce directional durotaxis. Reprinted from *Biophys. J.*, **97**, Isenberg, B. C., *et al.*, Vascular smooth muscle cell durotaxis depends on substrate stiffness gradient strength, p. 1313, Copyright (2009), with permission from Elsevier.[145]

Controlling display of the plurality of biochemical interactions in ECM is also an emerging opportunity. Synthetic scaffolds often adopt a reductionist strategy by presenting only a single adhesive peptide such as RGD, or perhaps 2–3 additional cell-instructive cues. This simplification overlooks the well-documented synergistic effects of ligand co-presentation. For instance, co-display of RGD with PHSRN has been shown to enhance integrin α5β1 signaling compared to either motif alone.[41] Similarly, incorporating collagen-mimetic GFOGER sequences can specifically recruit α2β1, directing different adhesion and differentiation outcomes than RGD alone.[17] Cavalcanti-Adam and colleagues demonstrated that co-immobilizing RGD with BMP-6 on nanopatterned surfaces enhanced myoblast transdifferentiation by promoting localized and sustained cell signaling.[19] This aligns with a broader body of work showing that ECM ligands and growth factor–binding domains act cooperatively to regulate cell fate, often through precise nanoscale co-presentation. Beyond integrins, glycosaminoglycans such as heparin sulfate display a range of growth factors, which stabilize spatial gradients and prolonging receptor engagement.[3] Thus, a diversity of ECM components act synergistically to support and direct cell phenotype and tissue development and healing outcomes, suggesting the need to increase the complexity of ECM mimics to match that level of spatial and biochemical complexity.[6]

Conclusions and outlook

Effective mimicry of ECM lies along multiple interrelated axes. Spatial hierarchy influences biochemical display, energetic landscapes, timescales of reorganization, static and dynamic mechanics, linear and nonlinear viscoelasticities, biochemical function through crowding, cellular invasion, and mass transport. In turn, cellular behavior drives, and is itself dictated by, intersections with those hierarchical axes. Those cellular behaviors then determine the fate of any tissue development, healing, or remodeling process. Thus, it is vital that future developments in ECM mimicry address these intersections. ECM-like spatial organization without dynamic reorganization on cellular time and energy scales may be too static. Reconfigurable materials without appropriate energetic feedback loops to proliferating and differentiating cells are unlikely to fully recapitulate the milieu needed for complex tissue formation. Dynamic materials that only respond in discrete time regimes will not fully capture the multiscale dynamics present in natural ECM.

Thus, we can point to some key opportunities and challenges for next-generation ECM-mimetic materials:

• Considering temporal dynamics, how can one design materials that couple cell:material interactions at the nanoscale to both reversible and irreversible material changes across a range of timescales?

• Through the lens of energetics, how can one couple the relevant energies exerted by cells at the nanoscale to energetic dissipation at longer length scales in a predictable and biointegrative fashion?

• When considering molecular and nanoscale crowding, how does one overturn the current paradigm that focuses on porous, cell-permissive networks to instead engineer molecularly crowded environments that more faithfully mimic ECMs regulation of biomolecular, biophysical, and cellular processes. How can materials with nanoscale crowding permit facile cell migration, tissue remodeling, nutrient diffusion, and efficient cellular energy usage?

• When tailoring the nanoscale display of biomolecules, how does one engineer materials that display cell-instructive motifs in 3D while simultaneously coupling those display sites to the temporal, energetic, and biophysical hierarchy of ECM?

• Finally, what future material platforms will serve as the canvas upon which we can display all these features and functions simultaneously, in a manner that is customizable for specific tissues and indications, within a framework that is easily translatable to clinical use?

As noted above, many of the areas where development of new materials is hindered relates to the gap between molecular level control and micron-scale structure – or the nanoscale regime – where dynamics, crowding, mechanics, and reconfigurability in ECM dictate a significant degree of function. Harnessing these factors at the nanoscale while seamlessly integrating across the entire hierarchy of tissue structures remains a challenge and represents a significant opportunity for future researchers in the domain.

Author contributions

All authors contributed equally to the writing, review, and editing of this manuscript.

Conflicts of interest

There are no conflicts to declare.

Data availability

No primary research results, software or code have been included, and no new data were generated or analysed as part of this review. Raw data from the bibliometric analysis will be made available upon reasonable request.

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