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Engineering biomimetic and instructive materials for wound healing and regeneration

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Abstract

Development of biomimetic and instructive materials is emerging as a promising approach for redirecting fibrotic wound healing into a regenerative process. In nature, complete tissue regeneration can transpire in certain organ substructures, during embryogenesis and, remarkably, in some organisms in which whole limbs can regrow. These regenerative phenomena were observed to possess specific extracellular matrices, as well as stem cell niches and regulatory signaling pathways, that likely act as spatiotemporal organizers of these preferred outcomes. Biomimetic materials are now improving on the limitations of existing wound care treatments because they are being designed to stimulate these spatiotemporal cues, thus supporting regeneration within host tissues. A variety of novel materials have already emerged and demonstrated promise both in preclinical studies and in patients. This review discusses the recent advances in understanding these biomimetic and instructive properties and their integration into wound care scaffolds.

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Introduction

Regeneration is a mechanism whereby a tissue, an organ, or a whole body part can recover its original structure and function after an injury or disease. Although this mechanism is observed in humans, it typically shows a marked decline in potency with increasing age and is restricted to specific tissues. Interestingly, some organisms have revealed remarkable capacity to repair and regenerate tissues throughout adulthood in ways that resemble developmental processes [1]. Most notably, some amphibians can regenerate entire limbs through the formation of a blastema composed of lineage-restricted progenitor cells [2]. In mammals, the African spiny mouse was recently discovered to exhibit regenerative ability, restoring skin architecture and appendages in a similar blastema formation process [3]. Other mice commonly used for preclinical studies were also reported to regenerate hair follicles in full-thickness wounds via recruitment of epithelial progenitor cells in the surrounding uninjured epithelium and hair follicle bulges [4]. Humans in contrast hold such regenerative capacity early in development (up to the end of the second trimester), where particular cellular and extracellular matrix (ECM) constituents drive wound closure and restore tissues to their native states [5]. Although the mechanisms that direct these remarkable events remain to be completely explained, a growing understanding of the different proregenerative pathways is being established. Notably, various published reports now suggest that the ECM is an instructive substrate [6,7], acting as a spatiotemporal organizer and controller for growth, homeostasis, repair, and decay.

Early in development, the wound healing process has demonstrated the capacity to heal in a regenerative manner, where damaged tissues are restored to their original, *scarless* configurations. First discovered in fetal lambs in 1971 [8], these observations were later confirmed in several other organisms including mice, rats, pigs, monkeys, and humans [9]. Comparative studies on developing fetal tissues and adult skin have now enabled quantification of key differences in cellular and extracellular compositions, thus gradually shedding light on the mechanisms that drive scarless wound healing. For example, recent lineage-tracing studies in mice have identified two distinct embryonic fibroblast lineages: one found early in development that supports tissue regeneration and another predominant during late-stage development and adulthood, which is responsible for tissue scarring [10–12]. Strategies targeting these fibroblast lineages have already demonstrated efficacy in reducing scar formation. The extracellular environments that support these cell

populations have also exhibited measurable differences through development and adulthood and are likely reinforcing, or even modulating, these fibrotic and antifibrotic phenotypes [12]. ECM molecules prevalent in fetal tissues, such as fibronectin, hyaluronic acid, and collagen III [13], have in particular demonstrated regulatory influences on wound healing–relevant cell behaviors [14,15] that trigger tissue regeneration in both space and time [5].

From a clinical perspective, basic requirements for wound dressings generally include hydration regulation, pathogen protection, shape conformation, ease of use, and cost-effectiveness. These specifications have led to the development of widely used synthetic dressings, such as Tegaderm™ and Opsite™, which are effective in protecting wounds and enabling wound closure; however, these products remain suboptimal for accelerating wound closure and stimulating tissue regeneration—especially in more severe injury scenarios [16,17]. In contrast, when wound care materials are designed as *instructive* systems [18] or even as replacement strategies [17], additional components are incorporated and tailored to address these limitations. Biochemical, mechanical, and structural properties that mimic key aspects of the targeted tissues and mechanisms for controlled degradation, aimed at enabling rapid tissue integration and ingrowth, are usually developed. To sustain cellular–material interactions and integration with the surrounding tissue, incorporation of structural cues and cell-binding moieties is commonly required. Preliminary studies investigating the potency of such biomimetic and instructive materials suggest great potential [18].

This review is focused on tissue repair in skin, examining its characteristic properties and inherent reparative ability during development and in adulthood. In parallel, it surveys different strategies aimed at designing this new class of instructive biomimetic systems, albeit still early in their inception. Specifically, this review discusses how properties of these proregenerative materials—whether mechanical, biochemical, or structural—can influence endogenous repair and how the interfaces of these systems require tissue-specific tailoring for adequate repair and regeneration.

Understanding ECM-biomimetic features for biomaterial design

Every tissue in the body has a unique set of cells and ECM proteins arranged into a distinctive architecture [19], thus requiring the properties of bioengineering scaffolds to be designed in an organ-specific way. These properties (Figure 1), be they mechanical, biochemical, or structural, can independently or synchronously have a significant influence on cellular behavior and function and therefore need to be chosen carefully when designing a material for tissue engineering or regenerative medicine applications.

Mechanical properties for proregenerative scaffolds

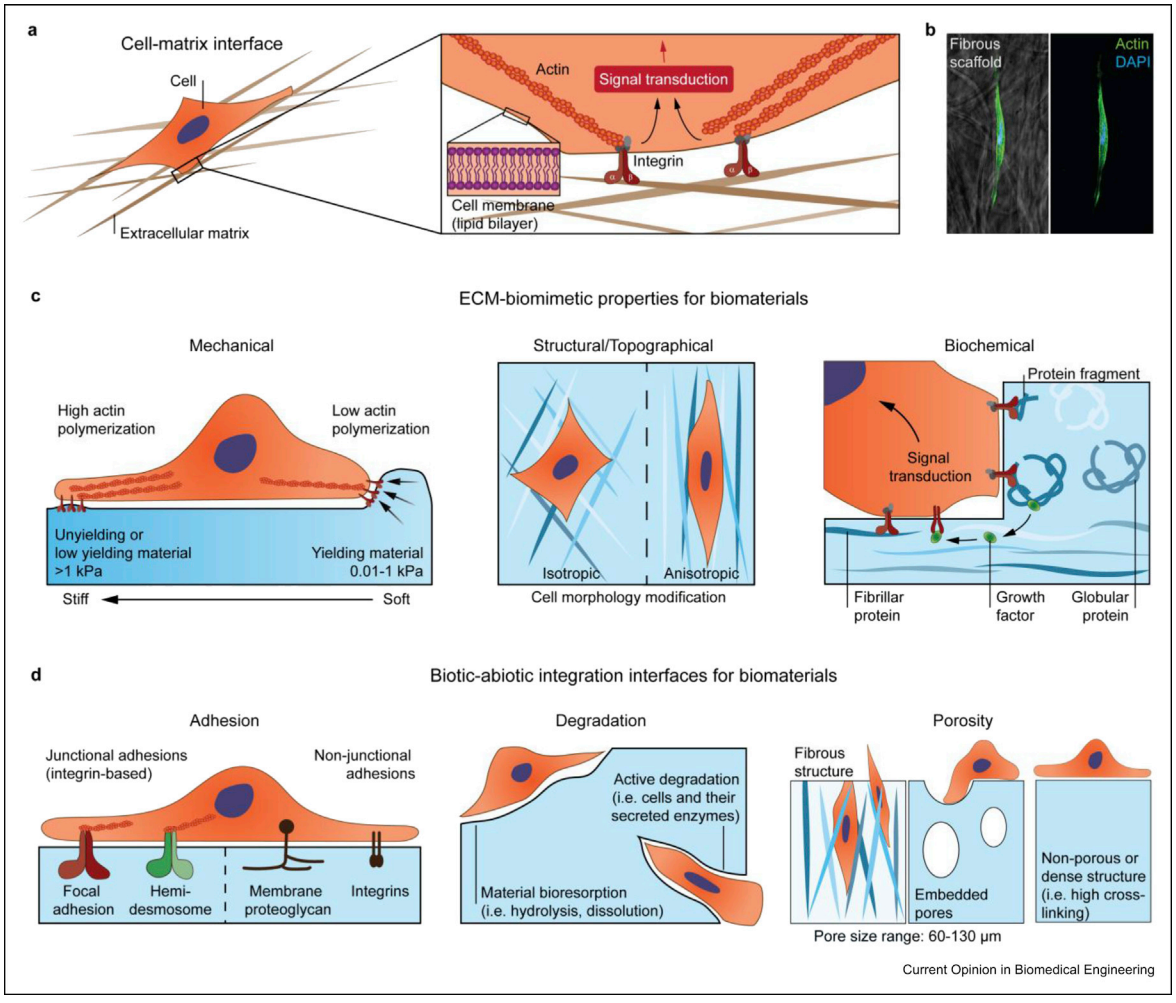
The mechanical properties of skin—imparted principally by the dermal layer—will typically range from 0.8 to 1.2 kPa in adult human tissues (measured in compression), with differences associated with body area and age [20]. Similarly, fibrotic tissues and scars, established after injury, are remodeled into stiffer and less elastic tissues than normal healthy skin [21]. These differences are caused by alterations in the composition, concentration, and architecture of ECM components, as well as further post-translational modifications that include glycosylation, transglutamination, and cross-linking [21–23]. Although it remains unclear how these changes—hallmarks of fibrotic tissues—can be treated, it has now become apparent that mechanical cues are implicated in pathological stiffening and should therefore be taken under close consideration.

Studies of the 1980s and early 1990s started elaborating on this idea when it was first hypothesized that the ECM involvement in cellular regulation and function was more than just structural support [24]. This led to the inception of concepts such as *dynamic reciprocity*, explaining the continuous regulatory feedback between cells and their surrounding ECM [25], or *mechanotransduction* that illustrated the conversion of mechanical signals into biochemical responses [26]. In the context of wound repair and regeneration, these mechanoprocesses helped to explain key differences in wound pathophysiology [27,28]. ECM-derived wound dressings, such as the *Alloderm™ Regenerative Tissue Matrix*, engineered via a top-down decellularization approach, have held in that regard an advantage as they inherently mimic the mechanical properties of their target tissue (Figure 2). However, the limited ability to uncouple these properties from their biochemical content has offered limited insight into the underlying mechanism driving their preferred outcomes. The development of synthetic hydrogels with orthogonal control over substrate stiffness and adhesive ligand density has now permitted to evaluate these biomimetic properties independently from one another. It was, for example, discovered that high scaffold stiffness promoted fibroblast proliferation and stress fiber formation, associated with a typical fibrotic response, while compliant matrices supported stronger angiogenic activity [29]. In biomimetic fibrous scaffolds, lower stiffness supported increased local reorganization of the material, thus supporting formation of focal adhesions via concentration of adhesion ligand density at the cell surface [30]. Assembly of such adhesion complexes is central to several mechanisms of wound healing [31] and may even be leveraged to enhance them [32]. Altogether, these mechanobiology studies provide strong evidence that

appropriately defining the mechanical environment in the wound will be critical in stimulating a regenerative response. Skin stiffening during development and aging may lead to decreased healing capacity, but may also be an active regulator of fibrosis progression [33]. Softer materials on par with fetal skin, where regeneration is commonly observed [5], may thus be preferred for designing more potent proregenerative wound dressings.

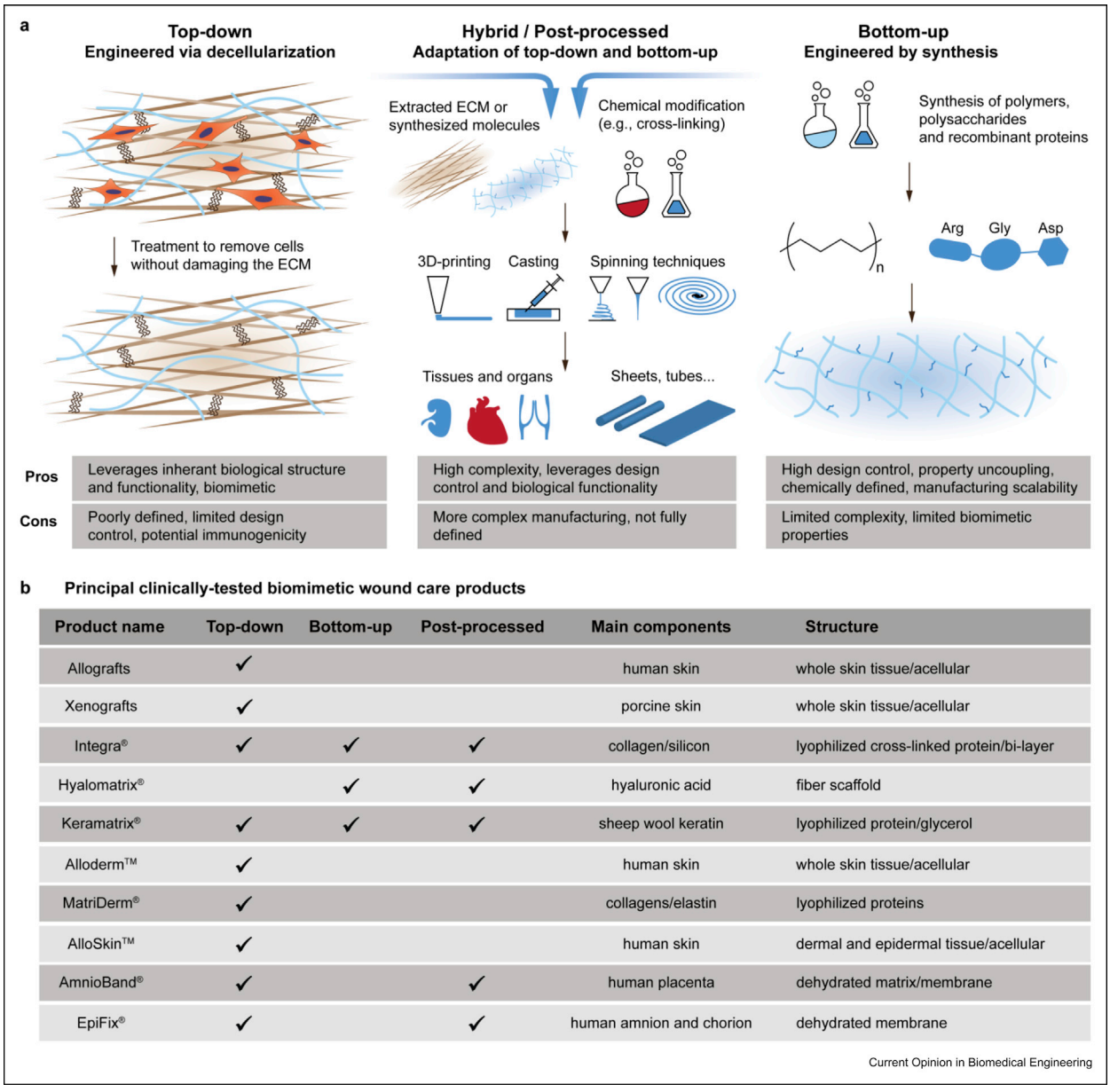
Several mechanomimetic materials have already been investigated for wound healing and other regenerative medicine applications. Hydrogels developed from polyethylene glycol, dextran, alginate, chitosan, cellulose, or hyaluronic acid can be cross-linked through various methods to modify their stiffness regimes. Such bottom-up approaches demonstrated promising results in stimulating wound closure and tissue regeneration in skin [34–37] and in other organ pathologies (e.g. myocardial

Figure 1



Regulating cell function using instructive ECM-biomimetic scaffolds. **(a)** Schematic illustrating the cell–matrix interface: a cell surrounded by its extracellular matrix (ECM) environment. The inset shows a typical cell–matrix interface, mediated by integrin transmembrane proteins, which connect to intercellular proteins, such as cytoskeletal actin. The activation of integrin caused by external stimuli will enable transduction of the signal across the cell membrane that will in turn affect cell behavior. **(b)** Immunofluorescent images (left: merged with bright field) of a dermal fibroblast adopting its shape to a fibrous scaffold. **(c-d)** Schematics of key ECM-biomimetic properties (**c**) and biotic–abiotic integration interfaces (**d**) that can be harnessed to achieve desired cell behaviors and cell fates in a damaged tissue for improved repair. (**c**) Mechanical: cells modify their cytoskeletal structure (e.g. via actin polymerization) differently depending on substrate stiffness, leading to overall changes in behavior and fate. Soft substrates can likewise be remodeled by the cell. Structural: cells adopt or rearrange their morphology according to the substrate structure and topography. Biochemical: cells are influenced by the biochemical content of their surrounding ECM as they bind to different proteins and other extracellular molecules. Proteins (e.g. fibronectin) can, furthermore, be found in different conformations (globular and fibrillar) or broken down into minimal function units (fragments), while proteins can sequester growth factors, all of which affect cell behavior. (**d**) Adhesion: cells can bind to a substrate using a variety of adhesion mechanisms, including both junctional (via integrins connected to actin or keratin) and nonjunctional mechanisms (via nonconnected integrins or integral membrane proteoglycans). Degradation: cells can integrate a scaffold by actively degrading it or by controlled bioresorption of the material upon implantation. Porosity: cells can infiltrate a fibrous scaffold or scaffold with embedded pores of sufficient pore size (this is a cell-dependent property). By contrast, a nonporous or dense scaffold will typically hinder cellular infiltration and therefore integration upon implantation. DAPI, 4′,6-diamidino-2-phenylindole.

Figure 2



b **Principal clinically-tested biomimetic wound care products**

Product name	Top-down	Bottom-up	Post-processed	Main components	Structure
Allografts	✓			human skin	whole skin tissue/acellular
Xenografts	✓			porcine skin	whole skin tissue/acellular
Integra®	✓	✓	✓	collagen/silicon	lyophilized cross-linked protein/bi-layer
Hyalomatrix®		✓	✓	hyaluronic acid	fiber scaffold
Keramatrix®	✓	✓	✓	sheep wool keratin	lyophilized protein/glycerol
Alloderm™	✓			human skin	whole skin tissue/acellular
MatriDerm®	✓			collagens/elastin	lyophilized proteins
AlloSkin™	✓			human skin	dermal and epidermal tissue/acellular
AmnioBand®	✓		✓	human placenta	dehydrated matrix/membrane
EpiFix®	✓		✓	human amnion and chorion	dehydrated membrane

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Approaches for engineering instructive ECM-biomimetic scaffolds. **(a)** Top-down approaches leverage the inherent mechanical and structural properties, as well as the biochemical makeup of a tissue to promote tissue repair. These approaches involve decellularization using various chemical and physical methods, thus providing an acellular tissue. Bottom-up approaches by contrast are developed from synthesis of minimal functional units, such as monomers, saccharides, and amino acid sequences, and assembled into integrated functional systems. Hybrid approaches regularly combine methods from both top-down and bottom-up to design highly functional and integrated systems. They include methods for processing these components into sheets, tubes, and more complex structures such as tissues and organs, using a variety of manufacturing techniques, such as 3D printing, casting, and spinning. **(b)** Table detailing the principal clinically available biomimetic wound care products, their method of fabrication, main components, and structure. Information adapted from www.woundsource.com. ECM, extracellular matrix.

infarction [38]). A competing approach has consisted in using proteins derived from biological tissues such as collagen, fibrin, or elastin and is now routinely found in clinically available dressings and skin substitutes [17]. Here, these scaffolds can be processed (structurally or chemically), while directly leveraging the inherent tissue-level mechanics of their biologically derived materials. It should however be reiterated that while targeting the ECM stiffness is an emergent clinical strategy to attenuate fibrosis for multiple pathologies [23], there is still limited evidence as to how these mechanical cues are influencing regeneration in skin.

The progress in developing highly tunable materials that facilitate property uncoupling should hopefully address this shortcoming.

Biochemical properties for proregenerative scaffolds

The ECM that constitutes the dermal layer—endowing it with its characteristic strength and elasticity—is predominantly composed of collagen type I and III [39]. Elastin and other glycosaminoglycans such as hyaluronic acid and chondroitin sulfate are also found in lower amounts in dermal tissue [13]. The biochemical composition of dermal tissue has also been shown to evolve through development and aging [5], contributing to the changes in tissue mechanics and function (e.g. hair loss [40]). While it remains unclear to what extent these variations are influencing wound healing and regeneration, these observations are suggestive of a biochemical regulatory relationship.

Accordingly, studies focused on understanding the role of these ECM proteins in multiple cell- and tissue–level processes have been conducted to improve the effectiveness of wound care therapies. Beyond their built-in mechanical properties, ECM molecules possess numerous additional regulatory features as they can bind to one another, to cells, and to soluble growth factors and are capable of orchestrating complex, multivalent signals [41]. Isolating or recombinantly engineering protein sequences has thus been useful in understanding the functionality of small peptides separately from their full-length proteins. The amino acid sequence arginine–glycine–aspartate (RGD), for example, has been extensively used in bioengineering studies and in regenerative medicine applications (Figure 2). A functional peptide found in laminin was similarly used to accelerate wound healing in mice [42], demonstrating promising results in wounds of diabetic mice. These peptides present several advantages as they are cheaper and better characterized; however, their restricted functionality may limit their biomimetic potential [18]. Studies have therefore also used ECM proteins in their full length to define, for example, the biochemical components necessary for driving stem cell expansion, lineage specification, or tissue morphogenesis [43]. Few studies have however focused on elucidating the respective contributions of these biochemical properties in the context of wound healing as improved outcomes can expectedly be achieved with more integrated systems.

Biochemical mimetics has therefore primarily relied on histological analyses to instruct proregenerative material design. As the most abundant ECM protein in adult skin, collagen type I has become widely used for tissue engineering applications and wound healing products [17,18]. However, being the principal component of scar tissue, the use of this protein has been questioned as collagen-rich tissue may not only be a consequence of fibrosis but also a driver of the pathology [33,44]. Existing collagen type I–based treatments have shown efficacy in supporting tissue formation and wound closure (for chronic wounds and burns); however, they may remain to be poor material choices for elaborating truly regenerative strategies. During embryogenesis, skin is supported by a matrix rich in collagen III, hyaluronic acid, and fibronectin—softer and more malleable molecules—and gradually transforms into a stronger and stiffer collagen I–dominated tissue [5]. Inspired by this evidence, several variations of hyaluronic acid–based hydrogels have been investigated with promising in vivo results [37,45]. More recently, a study has reported that scaffolds fabricated from decellularized neonatal tissues significantly improved the fibrotic outcome in an excisional mouse model [12]. Similarly, proteins extracted from embryonic skin rendered skin fibroblasts competent to regenerate functional hair follicles [46]. In a bottom-up approach, we engineered fibronectin nanofiber scaffolds, thus emulating the unique microenvironment of early embryogenesis. These scaffolds accelerated wound closure, and reduced scar severity, with evidence of de novo skin appendage regeneration at the center of the wounds [47]. Fibrillar fibronectin, fabricated using an alternative method of spontaneous self-assembly, was additionally reported to significantly enhance morphogen delivery, thereby driving full regeneration in bone [48]. Leveraging ECM proteins as vehicles was similarly investigated with laminin in the context of skin wound healing [49]. Biomimetic approaches such as these, leveraging both recently uncovered biological mechanisms and advances in materials science, should provide exciting development for the wound care field.

Structural properties for proregenerative scaffolds

In healthy skin tissue, the dermal collagen fibers are organized into a *basketweave* structure, with fibers typically oriented at a $\pm 45^{\circ}$ angle from a horizontal plane and intersecting each other perpendicularly [50]. Disruption of this distinctive architecture, caused by aging, disease, and fibrosis, will lead to more aligned collagen fibers. As a consequence, skin will suffer from weaker and less elastic mechanical properties [21]. By contrast, during embryogenesis, skin tissues revealed to be more porous than both scarred and healthy tissues [12]—an extracellular environment that would appear well adapted to tissue remodeling and repair.

Elucidating the role of ECM structures on numerous cell- and tissue-level functions has already generated some valuable insight. Micropatterning ECM proteins on culture substrates enabled us, for example, to demonstrate that restricting a cell to a specific shape can control cell morphology, cytoskeletal arrangement, and differentiation [51,52]. Different cell types will

furthermore respond differently to these particular shapes [53]. Remarkably, topographical features at subcellular size scales (down to nanometer size) can likewise influence cells [54] and be leveraged to mitigate fibrosis [55]. Conversely, three-dimensional (3D) substrates of various shapes and structures have also enabled to direct more complex tissue morphogenesis with pseudo-organ functions to be directed. Using nanofibers assembled into large sheets, we recently demonstrated the differentiation and maturation of myocytes into contractile muscle tissues. Fiber anisotropy was here a prerequisite to efficiently guide tissue assembly and maturation [56,57]. Accordingly, designing the appropriate structural cues requires careful consideration for optimally stimulating the various cell types that reside within the skin.

Numerous structural mimetic systems have been explored to manipulate cells and tissues in a regenerative manner in situ. Because of the fibrillar nature of most ECM proteins surrounding cells in the body, and specifically the proteins in the skin, using fibrous substrates has emerged as a primary focus. Various approaches have therefore already been explored, including tissue decellularization [58], molecular self-assembly [59], or spinning techniques [60], all with their respective advantages. Decellularization of human dermal tissues has provided relevant biomimetic scaffolds as they typically retain their fibrous, 3D structure, and ECM composition. This approach has enabled the clinical translation of products such as Alloderm™ and DermaMatrix™, widely used for treatments of severe wounds and burns and considered by some as the best available skin substitutes [17,61]. However, to what extent these developmentally mature matrices can activate endogenous stem cell niches to regenerate healthy skin structures remains unclear. Other unanswered considerations, including ECM protein deterioration and immunogenic responses [58,62], have drawn research efforts in the last decade toward more bottom-up and hybrid approaches. Spinning techniques, for example, that rely on electrical and mechanical forces to drive formation of nanofibrillar and microfibrillar structures from natural and synthetic polymers, are promising as they permit control over fabrication parameters and reproducibility [60,63]. These platforms can furthermore be scaled for rapid and on-demand manufacturing of tissue engineering [64] and proregenerative scaffolds [65], while their fabrication tunability has enabled to some degree recapitulation of the structural properties of native skin [36,47]. To enhance their functionality, these structural mimetic systems can be harnessed as vehicles for growth factor delivery, thus accelerating wound healing and improving tissue repair [66]. Conversely, molecular self-assembly, defined as spontaneous assembly of individual molecular components into an organized pattern or structure [59], can achieve control over fiber formation to an even lower nanometer range. Fibers of less than 10 nm doped with epidermal growth factors have, for example, significantly accelerated wound closure in an in vitro model [67], while ultrashort nanofibrous scaffolds showed promising results in partial-thickness burns [68]. Their small fiber size may facilitate in situ remodeling and could subsequently promote enhanced tissue regeneration. Altogether, these competing approaches have developed a diverse set of structural properties, with relative control and reproducibility. Moving forward, developing a better understanding of which properties to specifically target and promote will be critical in manufacturing more potent structural mimetic materials.

Biotic–abiotic integration interfaces in biomaterial design

The interfaces between the host tissue (biotic) and the applied proregenerative material (abiotic) are critical for achieving successful integration (Figure 1). Designing an extracellular environment that is instructive for tissue regeneration will not demonstrate efficacy unless a controlled invasion by the host cells is facilitated. Material resorption or biodegradation will here be mediated in parallel with tissue integration and regeneration. Accordingly, whether strategies are focused on full-thickness skin substitutes or simpler acellular biomaterials, designing the appropriate biotic–abiotic interfaces will be required.

Cell–matrix adhesion ligands

To regulate infiltration of cells in a scaffold, cell–matrix adhesion ligands are typically required. They enable cells to adhere to an extracellular substrate and further coordinate transmission of signals from the matrix to the cell and vice versa. Integrins—routinely used to bind these adhesion ligands—are transmembrane heterodimers that transmit mechanical and chemical signals across the cell membrane in both directions. Several ECM proteins, including fibronectin, vitronectin, collagen, and laminin, contain these integrin-binding ligands [69] and have accordingly been investigated in their full-length sequences as the principal building blocks of wound dressing materials [18]. Cross-linked collagen, derived from bovine tendon, is, for example, one of the principal components of the *Integra*® dressing and is leveraged to facilitate cellular invasion and capillary growth of the wound bed in preparation for the application of split-thickness skin grafts [70]. In our work, we engineered nanofiber scaffolds from fibronectin proteins that integrate RGD. These scaffolds exhibited almost complete tissue integration within the host 6 days after application, suggesting an efficacious cell–matrix interfacing [47]. Alternatively, minimal amino acid sequences have in the last decade emerged as a popular approach for incorporating adhesion ligands into scaffolds. Synthetic hydrogels have relied on these

peptide sequences to engineer cell-adhesive materials. Injectable polyethylene glycol (PEG) [35] and fibrin [71] materials, with covalently bound RGD peptides, significantly accelerated wound closure, while initiating rapid revascularization of the underlying tissues. To address the limited specificity of these peptides, hydrogels have been engineered to promote precise integrin engagement, revealing clear improvements in the context of tissue repair [72]. Looking ahead, these and other ligands can be presented in a temporally and spatially controlled manner using photopatterning, both in hydrogels [73] and in fibrous biomimetic scaffolds [74]. Leveraging these new capabilities for mimicking and targeting heterogenous tissues should prove promising as interfacing approaches.

Degradation properties

Central to regenerative medicine approaches is the capacity for materials to be gradually replaced by the host cells and ECM, thus accommodating tissue neogenesis. These materials need to naturally dissolve or be amenable to biodegradation, whether via enzymatic or hydrolytic reactions, without releasing toxic by-products [75]. In the wound, this occurs when the provisional fibrin matrix is proteolytically degraded by invading dermal fibroblast and endothelial cells that require space to migrate, proliferate, and lay down their own ECM. Synthetic hydrogels, in a biomimetic manner, are increasingly being engineered to degrade by incorporating peptide cross-linkers susceptible to protease cleavage. In the presence of matrix metalloproteinases (MMPs) produced by cells, these peptides are cleaved, thus permitting a cell-mediated degradation [76]. While hydrogels can typically degrade hydrolytically, these cell-mediated strategies have proven advantageous as they permit remodeling directly by the invading cells. This prevents materials from degrading too fast, leaving cells without a scaffold to infiltrate or, too slowly, preventing cells from remodeling and regrowing the damaged tissue. MMP-sensitive peptides have more recently been integrated into biomimetic fibrous materials, permitting a gradual degradation upon subcutaneous implantation in mice [77]. To further capture the dynamic properties of the native ECM, reversible chemical bonds can be incorporated into materials, thereby providing better temporal control over infiltrating cells [78]. Altogether, whether an engineered approach is used or the inherent properties of the implanted material are leveraged, tailoring the degradation kinetics to a specific tissue needs be considered as this property was shown to regulate stem cell fate [79].

Porosity and topography

Designing materials with pores can further improve the cellular integration by the host. Indeed, although protease-degradable scaffolds should permit endogenous invasion, increasing the material porosity in a reasonable manner could significantly accelerate this process. With this approach, host cells are not required to continuously produce MMPs to migrate and proliferate through a scaffold, thus permitting faster infiltration. MMP-sensitive hydrogels with and without micropores have indeed exhibited a market difference in tissue integration after 24 h only [35]. In vivo, the same hydrogels promoted significantly faster wound closure, whereas the nonporous gels (while still MMP-sensitive) displayed even worse outcomes than the nontreated controls. These observations underscore the importance to appropriately tailor porosity. To further mimic the native ECM, microparticle hydrogels are now being leveraged to incorporate heterogeneous properties, including porosity and scaffold mechanics, for a more potent in situ modulation [80]. Here, engineering fibrous materials is an otherwise obvious approach as porosity can be tailored by changing spinning parameters [65], while fiber orientation can guide tissue morphogenesis or migration directionality. By contrast, top-down approaches such as decellularization which have limited control over porosity may present limitations in certain instances. A decellularized matrix of the mature skeletal muscle—with a characteristic tubular network structure [81]—would appear poorly adapted for efficient tissue integration, while decellularized tissues for heart valve replacements have already demonstrated clinical success. Accordingly, porosity should be addressed carefully and in a tissue-specific manner.

Discussion and future perspectives

With our recent advances in engineering, we are now starting to leverage our understanding of complex phenomena in nature to develop truly designer approaches aimed at achieving complete tissue restoration. Across the eukaryotic taxon, multiple organisms are indeed capable of impressive tissue regeneration abilities that likely evolved as a function of their unique behaviors and habitats. Research has been able to identify key mediators enabling these regenerative phenomena, while understanding how they might translate to human biology. Tissue engineering and regenerative medicine studies both in vitro and in vivo have furthermore provided some additional insight as to how material approaches should be designed. Separated here into two categories, we have reviewed how *biomimetic features* and *biotic—abiotic interfaces* can be leveraged for engineering instructive proregenerative solutions. Not unsurprisingly, we also found that wound healing and regenerative medicine studies have yet to more comprehensively explore some interesting questions that originated in basic cell biology research. These may include the following: Can substrate topography influence wound closure dynamics? How does substrate stiffness affect tissue repair? Can a scaffold's stiffness direct endogenous stem cell fate? The advent of highly tunable materials should likely enable some of these intriguing questions to be answered. In the context

of fibrotic pathologies, these questions have already enabled important findings to be uncovered. ECM stiffness has now emerged as a promising therapeutic approach for several pathologies, including idiopathic lung fibrosis, cancer, and multiple myeloma, and is now being investigated in a dozen different clinical trials [23].

For cutaneous wound healing and regeneration, several bioinspired advances have nonetheless already been developed including protease-mediated degradable hydrogels, nanofibrous scaffolds, and 3D-printed skin constructs. Clinically available skin substitutes, such as Integra® or MatriDerm®, are now already routinely used to support wound closure of severe wounds and burns but will still require additional improvements to enable complete tissue regeneration [17]. More recently, bottom-up, instructive approaches that incorporated degradation sites, cell–matrix adhesion ligands, biomimetic stiffness, micropores, morphogens, and immunomodulatory triggers have exhibited impressive results, even when compared with these commercial products [34,35,82]. Efforts are now being made to translate these technologies to the clinic. Moving forward, fine-tuning these biomimetic properties and biotic–abiotic interfaces may provide the necessary stimuli for attaining more potent results and hopefully complete tissue regeneration.

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Conflict of interest

Nothing declared.

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- • of special interest
- •• of outstanding interest

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