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Decoupling Polymer Properties to Elucidate Mechanisms Governing Cell Behavior

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Determining how a biomaterial interacts with cells ("structure-function relationship") reflects its eventual clinical applicability. Therefore, a fundamental understanding of how individual material properties modulate cell-biomaterial interactions is pivotal to improving the efficacy and safety of clinically translatable biomaterial systems. However, due to the coupled nature of material properties, their individual effects on cellular responses are difficult to understand. Structure-function relationships can be more clearly understood by the effective decoupling of each individual parameter. In this article, we discuss three basic decoupling strategies: (1) surface modification, (2) cross-linking, and (3) combinatorial approaches (i.e., copolymerization and polymer blending). Relevant examples of coupled material properties are briefly reviewed in each section to highlight the need for improved decoupling methods. This follows with examples of more effective decoupling techniques, mainly from the perspective of three primary classes of synthetic materials: polyesters, polyethylene glycol, and polyacrylamide. Recent strides in decoupling methodologies, especially surface-patterning and combinatorial techniques, offer much promise in further understanding the structure-function relationships that largely govern the success of future advancements in biomaterials, tissue engineering, and drug delivery.

Introduction

The tunability of chemical synthesis and material fabrication enables polymeric biomaterials to display diverse chemical and mechanical properties. This characteristic is crucial in developing materials for advanced biomedical applications, including tissue engineering, drug delivery, and medical device development. However, significant challenges remain in producing polymeric materials that can provide tissue-specific therapeutic effects for repair and regeneration by intricately controlling cell behavior in an effective manner, while minimizing adverse inflammatory and immunogenic effects. Determining how a polymer interacts with biological systems *in vitro* and *in vivo* reflects its clinical applicability, and a fundamental understanding of how individual material properties modulate cell-biomaterial interactions is essential for improving the efficacy and safety of clinically translatable biomaterial systems.[1,2]

Control over cell behavior through the regulation of cell-material interactions is a powerful approach for understanding how extracellular cues modulate the cellular response, at both the single-cell and tissue levels. When a biomaterial is in contact with a biological environment, water molecules surround the material within nanoseconds; and proteins are adsorbed to the surface in a surface property-dependent manner.[3] Cells then sense and attach onto the adsorbed proteins[4] by forming focal adhesion (FA) through specific interactions between cell-surface receptors (e.g., integrin) and extracellular ligands (e.g., arginine-glycine-aspartic acid: RGD). The cell-adhesive motifs are contained within extracellular adhesive proteins, such as fibronectin, vitronectin, collagen, and laminin.[3,5–7] Receptor-ligand interactions direct cell motility, morphology, and function[8,9] by mediating complex bi-directional signaling between cells and extracellular matrix (ECM)[10] through various chemo- and mechano-transduction pathways.[11–13] It is well established that biomaterial properties, such as chemical,[14] mechanical,[15,16] and topographical properties,[17,18] modulate cell and tissue responses to the biomaterials (e.g., structure-function relationships).[19,20] For example, hydrophobic materials tend to bind more proteins in a thermodynamically favorable manner, resulting in improved cell attachment and spreading, compared with hydrophilic materials.[21] In addition, the intrinsic mechanical properties of biomaterials have significant effects on cell attachment,[22,23] spreading, migration, proliferation,[24,25] and differentiation.[15,25–30] Cells respond to changes in the mechanical microenvironment in a cell type-specific manner, as the elastic modulus of tissues in the body ranges over several orders of magnitude from ~100 Pa in the soft tissue of the brain to ~100 MPa in bone.[31,32] Intracellular mechanical forces are generated as cells adhere to and migrate across a surface,

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resulting in alternation of the structure and composition of FAs.[3,30,33,34] A polymeric substrate should be stiff enough to resist these cell traction forces and maintain sufficient cell-material interactions; on the other hand, substrates that are too stiff hinder cell viability, presumably due to a lack of cell-cell communication.[3,30,35]

It has become increasingly clear that material properties influence one another and are, therefore, intrinsically coupled. For example, the chemical composition of a polymer largely determines the other resulting material characteristics, including crystallinity, hydrophilicity/hydrophobicity, and degradation. Improved crystallinity inherently correlates with enhanced polymer chain packing, thereby resisting water penetration and hydrolytic degradation. In addition, tightly packed polymer chains usually result in increased material stiffness. These facts indicate that the resulting cellular behavior is actually in response to the coupled material properties rather than individual ones. Therefore, there is an unmet need to decouple the material properties so that the effect of individual material properties on cellular functions can be clearly understood and exploited for an enhanced, precise regulation of cell behavior (Fig. 1).

This article aims at providing a comprehensive review of current methods for altering chemical and mechanical properties of biomaterials, especially in a decoupled manner, to design the most suitable micro-environment for control over cell fate. Three promising decoupling strategies are discussed: (1) surface modification, (2) cross-linking, and (3) combinatorial approaches (i.e., copolymerization and polymer blending). In each section, we first briefly review the relevant literature regarding the cellular response to coupled material properties to highlight the need for decoupling strategies, and then discuss the current strategies for decoupling chemical and mechanical parameters in similar systems. Although other types of material properties such as topography play a role in cell-material interactions[17,18,36–43] and some of the decoupling strategies can be extended to handle such delineations, we focus primarily on two dominant properties, chemical and mechanical. The purpose of this article is to reveal the limitations and issues associated with coupled polymer parameters, as they pertain to the control of cell behavior and establish a benchmark for decoupling strategies to foster advancements in biomaterials, tissue engineering, and drug delivery.

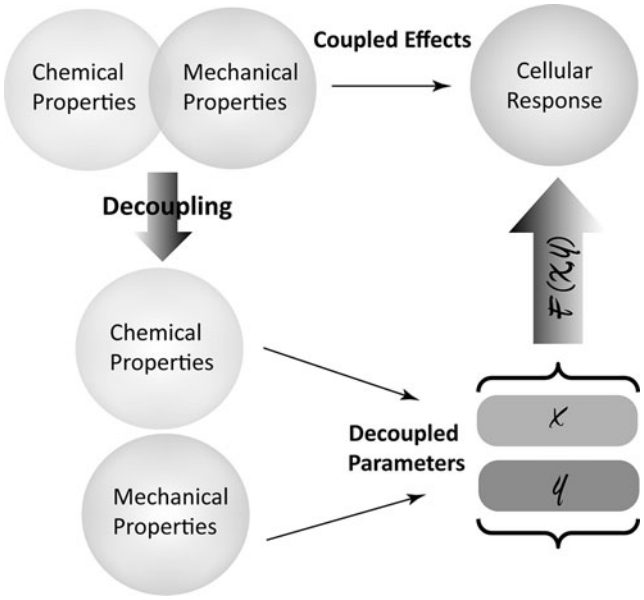

FIG. 1. Coupling and decoupling of polymer chemical and mechanical properties determine cellular response.

Necessity and Strategies of Decoupling Material Properties

Studying cell behavior in response to coupled material properties hinders the development of materials that can actively control cell function, because individual material properties could be more effectively optimized to modulate cell functions if understood as separate components. Decoupling strategies are, therefore, imperative to achieve a better control over cell functions by incrementally varying the chemical or mechanical properties while minimizing the collateral effects on other properties in order to elucidate the independent effects of each property. The decoupling approaches discussed next provide an insight for further improvement of these strategies and will enable the increased isolation of the effects of individual material properties on cell behavior, thereby providing a rational basis for the design and implementation of polymer scaffolds for specific applications.

Surface modifications

Covalent conjugation or simple blending of bioactive molecules into bulk polymer materials (e.g., scaffold) has been widely used to improve cell functions. For example, RGD can be covalently tethered to polyethylene glycol (PEG) chains to improve cell attachment,[44–46] and protease-sensitive peptides originating from collagen or fibrinogen can be conjugated to PEG cross-linkers for hydrogel degradation and remodeling by matrix metalloproteases (MMPs).[47,48] It is usually assumed that the impact of such peptide/protein modification on bulk scaffold properties is negligible, and, therefore, the enhanced cellular response is solely the result of chemical changes imparted by the surface modification; however, there are often appreciable changes in bulk scaffold properties.[49–52] For example, Zustiak *et al.* reported that the covalent attachment of ECM peptides (e.g., RGDS, IKVAV, and YIGSR) to PEG hydrogels changed the modulus, mesh size, swelling ratio, and albumin diffusivity of the bulk material.[51] Blending poly(lactic-*co*-glycolic acid) (PLGA) or poly-L-lactide (PLLA) with ECM-derived components (e.g., collagen, gelatin, and elastin) has been shown to improve cell adhesion and proliferation by changing the chemical composition, but resulted in changes to the mechanical properties as well.[53–57] In another example, collagen was incorporated into a poly(ε-caprolactone) (PCL) scaffold at different ratios to enhance human dermal fibroblast and epidermal keratinocyte proliferation.[58] Although similar morphological properties were observed as the fiber diameters remained constant for scaffolds containing 1% and 30% PCL, the stiffness of the nanofibrous scaffolds increased from 8.4×10^{-3} to 2.3×10^{-2} N/mm, while both cell proliferation and type IV collagen synthesis decreased significantly, indicating coupled chemical and mechanical effects on cell behavior.[58]

One way to address this interdependency is to introduce a coating of functional groups on the surface of a scaffold, generating a thin, activated, superficial layer that can minimize the alteration of bulk scaffold properties, as the modification only occurs at the surface. Chemical properties can be further fine tuned on this surface to enable efficient decoupling while maintaining bulk scaffold properties. The immobilization of bioactive molecules (e.g., ECM-derived peptides or growth factors), addition of chemical groups, or introduction of micro-patterns to the scaffold surface can, in many cases, dramatically alter surface properties and cell behavior without significantly changing bulk mechanical properties, indicating the successful decoupling of the surface chemical and bulk mechanical properties, as discussed next (Fig. 2).

Surface biofunctionalization with peptides and proteins. Several methods exist for chemically attaching peptides and proteins to the surface of a biomaterial scaffold. Chitosan and heparin have been covalently immobilized onto the scaffold surface of PLGA films using *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC) and *N*-hydroxysuccinimide (NHS), which improved hepatocyte adhesion and proliferation and decreased coagulation.[59] In another study, chitosan was immobilized to the surface of a PLGA scaffold by a photochemical reaction of azide-chitosan followed by the conjugation of gelatin, which strongly supported 3T3 fibroblast adhesion.[60] The same group reported that the surface modification of a PLGA scaffold with collagen could also be achieved by reacting with 1,8-diaminooctane and glutaraldehyde, which subsequently improved porcine smooth muscle cell proliferation.[61] Various growth factors, such as basic fibroblast growth factor and vascular endothelial growth factor (VEGF), can be further adsorbed to surface-immobilized heparin and collagen to provide the sustained release of these biomolecules.[62–64] The surface of PCL scaffolds has been functionalized with amine groups, which are further used to conjugate RGD motifs for the improved attachment of rat bone marrow stromal cells[65] and L929 fibroblasts.[66] Similarly, RGD has been covalently tethered to the surface of PEG scaffolds to improve cell attachment.[44–46] Polyacrylamide (PA), as an inert and anti-adhesive hydrogel,[67,68] can be used to decouple chemical and mechanical effects on cell behavior via the copolymerization of an active ester acrylate followed by the hydrolysis or replacement of the *N*-succinimidyl group with ECM-derived peptides, such as RGD.[69] Alternatively, ECM-derived proteins immobilized to the PA hydrogel surface via sulfo-SANPAH directed the osteogenic and myogenic differentiation of mesenchymal stem cells.[25]

Scaffold surface functionalization by plasma and chemical treatments. Instead of binding biofunctional molecules, the scaffold surface can be modified by adding chemical groups to improve cellular responses to biomaterial scaffolds. Various plasma treatments (e.g., O_2, Ar or NH_3) have been applied to change the surface-free energy and introduce hydroxyl, peroxyl, amine, or other functional groups to the surface of PLGA films, each of which subsequently impacted cell adhesion and proliferation.[70–72] Similarly, adhesion and proliferation of umbilical cord perivascular cells to a PCL scaffold was enhanced by increasing the density of surface carboxyl groups by grafting with poly(acrylic acid) using low-pressure plasma immobilization.[73] Apart from plasma treatment, chemical modification of the PCL scaffold surface using sodium hydroxide was shown to enhance surface hydrophilicity and improved the proliferation of endothelial and smooth muscle cells.[74,75] Finally, hydroxyl, carboxyl, or anionic surfaces have been introduced to derivatizable PA hydrogel surfaces to study cellular response to chemical cues.[76]

Surface patterning. Cellular responses can also be controlled by patterning the scaffold surface with cell-adhesive or nonadhesive molecules. The inert nature of PEG makes it an excellent substrate on which cell-adhesive or bioactive molecules can be patterned to confine cell adhesion,

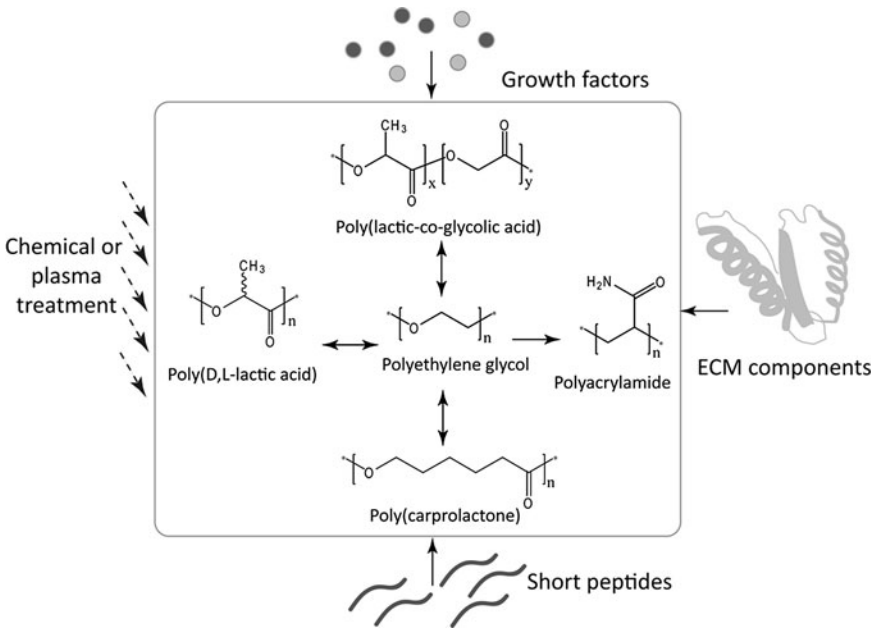

FIG. 2. Structures of polyethylene glycol (PEG), polyesters (polylactic acid, poly(lactic-*co*-glycolic acid), poly(ε-caprolactone)), and polyacrylamide (PA) as discussed in the article. Among these polymers, PEG plays a central role in copolymerization and also in tuning the properties of polyesters and PA gel. Polymer chemical properties can be further modified either by chemical or plasma treatment to introduce additional functional groups, or by incorporating extracellular matrix components, short peptides, and growth factors onto polymer chains.

migration, and differentiation to patterned areas. For example, RGD-modified islands were created by UV irradiation of PEG diacrylate-casted film surfaces through a photomask. Cells, therefore, only adhered and grew on the RGD-modified islands surrounded by nonadhesive cross-linked PEG.[77] The spatial neurite extension of cortical neurons was also controlled by confining the shape of cell-adhesive regions of poly-D-lysine with cell-resistant PEG materials (e.g., PEG-PDLA) lined up as barriers.[78] Interestingly, glass surfaces patterned with PEG dimethacrylate (PEGDMA) micro-wells promoted the differentiation of preadipocytes with increasing lipid accumulation, though it significantly increased the contact angle and decreased surface energy, making the surface less cell adhesive than unpatterned glass.[79]

Cross-linking

The degree of cross-linking can be varied to study the effects of substrate stiffness on cell behavior. However, in many cases, the manipulation of cross-linking often results in the change of chemical properties as well as the physical and topographical makeup of a material. For example, the concentration of EDC cross-linkers was varied to alter the elastic modulus in poly-L-lysine/hyaluronan (PLL/HA) multielectrolyte films, but unexpected changes to surface roughness and cell adhesion were observed in a coupled fashion.[80] Modulating the stiffness of PA gels by changing the bis-acrylamide cross-linker concentration has been used to create substrates with a physiological range of stimuli to mimic the stiffness of native tissue.[15] It was demonstrated that soft PA gels produced more dynamic, irregularly shaped FAs, whereas stiff gel stabilized FAs and reduced the migration of rat kidney epithelial and 3T3 fibroblast cells.[81] However, varying acrylamide and bis-acrylamide concentrations may expose different amounts of chemical moieties to cells, leading to unexpected cell responses (e.g., the cytotoxicity of acrylamide *in vivo*[82]). In addition, as the cross-linking degree increases, the pore size decreases within the gel network,[83,84] indicating the coupling of cross-linking and structural parameters.[85] In parallel, the intrinsic properties of PEG-containing hydrogels are coupled, as mesh size,[85] modulus,[86,87] and degradation rates[88,89] change with PEG content. A previous study demonstrated that PEGylation of fibrinogen reduced the MMP production and altered the normal spindle shape of neonatal human foreskin fibroblasts, which was likely due to increased hydrophilicty and repellence in coupling with reduced storage modulus.[90] In addition, changes in stiffness can be coupled with cell repellence and hydration in PEG-based hydrogels, which can drastically affect cell behavior.[86,91] The degree of cross-linking, PEG molecular weight (Mw),[92] and the type of cross-linker (i.e., PEG diacrylate [PEGDA])[85] can be altered to tune the modulus of PEG hydrogels. However, as stiffness increases, the swelling and diffusivity of PEG hydrogel decreases.[93] These coupled effects have been shown to impact ECM production and differentiation of mesenchymal stem cells,[94] illustrating another example of the need to decouple these properties for studying cell behavior.

The chemical and mechanical properties of cross-linked hydrogels can be decoupled by altering the types of the cross-linkers or the Mw of the polymers. For example, alginate hydrogels covalently cross-linked with adipic dihydrazide, methyl ester L-lysine, or PEG-diamine (1,000 Da) showed similar shear moduli within 31.1 to 36.9 kPa.[95] Alternatively, relatively constant stiffness can be obtained by varying the percentage of PEG monoacrylate (PEGMA) cross-linkers or the Mw of PEGDA in PEG hydrogels.[96] The Mw and hydrophilicity of PEGMA cross-linkers further refined this decoupling strategy to provide a tunable template for the independent modulation of stiffness and mesh size. Similarly, the incorporation of 4-arm PEG acrylate cross-linkers at various concentrations with the simultaneous tuning of the concentration and Mw of PEGDA enabled the decoupling of either the gel modulus or mesh size from a chemical composition.[97] VEGF expression and viability of fibroblasts was reported to be affected by both elastic modulus and mesh size, and the effect of the individual properties were identified through the aforementioned decoupling methods.[97] In another study, PEG methacrylate and poly(N-hydroxymethyl acrylamide) were cross-linked with oxidized methacrylic alginate (OMA) to control modulus and degradation rates.[98] Although degradation rate usually decreases with increased modulus, varying the number of oxidized uronic residues on OMA enabled controlled degradation rates with a relatively constant stiffness. Protein-release rates and subsequent angiogenesis *in vivo* were then regulated as a function of the OMA cross-linking.[98]

Combinatorial approaches: copolymerization and polymer blending

Altering the polymer composition is considered an important strategy that is employed for modulating matrix stiffness. However, a significant challenge still remains, as changing the polymer composition often results in simultaneous changes to hydrophobicity, crystallinity, and water uptake. For example, varying the blending ratio of PLGA and PLLA created a mechanical gradient to determine a "threshold stiffness" for optimal cell organization, myotubule formation, and myoblast differentiation.[30] The two polymers, however, have inherently different chemical properties that change simultaneously with the blending ratio, indicating coupling between chemical and mechanical properties. Similarly, PCL was blended with poly(ether sulfone) (PES) to study the influence of polymer stiffness on the differentiation of embryonic mesenchymal progenitor cells. A stiffer PES-PCL scaffold (modulus = 30.6 MPa) promoted osteogenesis, while a softer, pure PCL scaffold (modulus = 7.1 MPa) promoted chondrogenesis.[99] However, the change in chemical composition via altering the blending ratio was coupled with stiffness and should also be considered.

Although copolymerizing and blending different monomers or polymers often leads to simultaneous changes in other properties, these techniques can be used to decouple the chemical and mechanical properties by creating a combinatorial library of polymers and selecting compositions that display similar mechanical properties. Our recent study demonstrated that the wet elastic moduli of polymeric nanofibrous scaffolds were maintained within a tight range while altering the chemical compositions of co- or terpolymers through combinatorial synthesis and electrospinning techniques.[100] This unique approach enabled the synthesis of six polymer formulations with unique chemical characteristics but similar wet moduli. When cultured with

murine embryonic stem cells, they induced different levels of expression of intracellular hydrogen peroxide and cardiomyocyte markers, suggesting the effect of polymer composition on cell behavior, as the mechanical strength was maintained constant and decoupled. In addition, the copolymerization of PCL with other polyesters, such as polyglycolic acid and polylactic acid, have been shown to alter degradation, hydrophobicity, and crystallinity, while maintaining the elasticity exhibited by the pure PCL scaffold.[101–104] These examples demonstrate that the combinatorial synthesis of polymers is a promising approach for decoupling scaffold properties. The scale of the combinatorial library can be expanded to further tune a particular type of material property while minimizing the changes in other properties. A library of combinatorial polymers with 112 different compositions was produced from copolymerizing 14 different tyrosine-derived diphenols and eight aliphatic diacid monomers.[105] Changes in their chemical compositions were found to affect modulus, glass transition temperature (T_g), and contact angle. Polymers with a similar property (e.g., stiffness or T_g) could be grouped to study the cell response affected by chemical composition, demonstrating the effective decoupling of these properties.[105] Similarly, a library of poly(β-amino esters) (PBAEs) provided tunable mechanical, degradation, and adhesion properties. Degradation and mechanical properties were decoupled by varying Mw and branching structure.[106,107] Selected PBAE macromers were also cross-linked during electrospinning to improve the tunability of mechanical and degradation properties.[108] Such an approach was used to elucidate polymer structure-function relationships, thereby improving the safety and efficacy of their applications for gene delivery.[109,110] Similar approaches have been adapted to fine tune cellular responses to PCL acrylates[111] and methacrylate terpolymers.[112] An excellent review of combinatorial polymer synthesis techniques, high-throughput assessment of material properties, and material-cell interactions is thoroughly covered elsewhere.[113]

These combinatorial synthesis techniques offer distinct advantages over the traditional synthesis used for "one-measurement for one-sample" in terms of time, resources, and information to be obtained. However, there are still drawbacks and challenges associated with these methodologies, including the preservation of sample purity, data handling, and availability of such resources.[114] It is more challenging to use high-throughput schemes for sophisticated syntheses that require purification, and, in many cases, it is more worthwhile to test discrete polymer ratios to obtain data by a potentially more reliable method. Polymer blends can be used to circumvent such issues with synthesis, for instance, by observing cellular responses to gradient changes of polymer properties in a two-dimensional combinatorial library (e.g., temperature and polymer composition). For example, Sung *et al.* reported that a large library of PCL/PLGA blends with different stiffness, surface roughness, and/or crystallinity has been generated by varying the PCL-to-PLGA ratio and the annealing temperature, which provides an applicable approach for decoupling by selecting a group of blends similar in one property (e.g., stiffness) while differing in another (e.g., chemical composition). This study further demonstrated that a mid-to-high relative composition of PCL in a PCL/PLGA blend was ideal for smooth muscle cell adhesion, proliferation, and protein production.[115] Similarly, biomaterial microarrays can be used to decouple stiffness, cross-linking density, and crystallinity (Fig. 3)[116] and examine other chemical and topographical influences on various cell functions.[117–120] These combinatorial approaches offer much promise in elucidating the distinct mechanisms that govern cell-material interaction to further advance biomaterials and tissue-engineering technologies.

Conclusion and Future Direction

The field of biomaterials has witnessed a drastic expansion over the last few decades, but significant hurdles remain in clearly understanding structure-function relationships. A

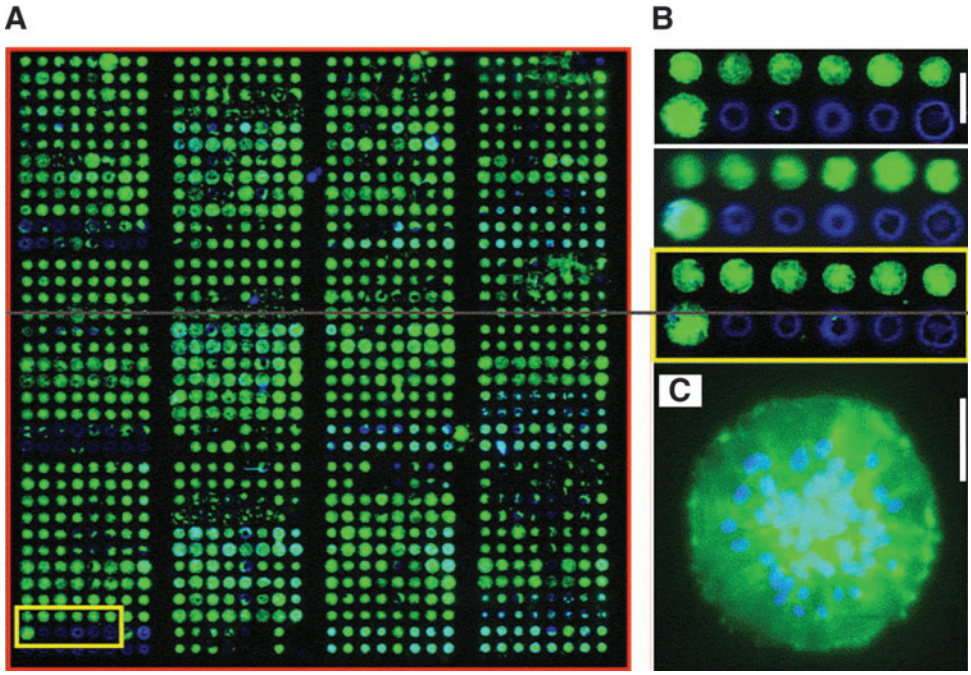

FIG. 3. Human mesenchymal stem cells grown on a microarray of combinatorial polymer blendings with various ratios of different polymers (adapted from reference 116). **(A–C)** cells on polymer microarray were fixed, and immunohistochemistry staining was performed for actin (green). Nuclei were stained with Hoechst (blue). **(B)** Close view of triplicates of polymer blendings highlighted in yellow squares in **(A)**, scale bar = 500 μm **(C)** Close view of polymer spots highlighted in yellow squares in **(B)**, scale bar = 100 μm. Color images available online at www.liebertpub.com/teb

major reason is that coupled material properties limit our understanding of how individual properties influence cellular response. For example, when the chemical composition of a polymer scaffold is changed by grafting biomolecules or altering the cross-linking density, other material properties such as stiffness, hydrophobicity, crystallinity, mesh size, and topography change simultaneously. Cellular responses to a material are regulated by the coupled effects of these interrelated material properties, making it difficult to interpret structure-function relationships. The decoupling of material properties is critical in determining how a change of a material property influences cell behavior. Although we primarily focus on decoupling chemical and mechanical properties, other influences such as physical and topographical properties are also vital to our understanding of cell-biomaterial interactions.

Promising approaches that are involved in decoupling chemical and mechanical properties are discussed and evaluated, which include (1) surface modification to create a superficial layer of functional groups, bioactive molecules, or micro-patterns; (2) cross-linking to specifically control chemical, mechanical, or physical properties independently; and (3) copolymerization to produce a library of combinatorial polymers with various chemical compositions, or blending of multiple polymers to create an array. Surface modification through chemical alternation (e.g., plasma or sodium hydroxide treatment) or the conjugation of bioactive molecules (e.g., ECM-derived ligands or growth factors) to create a superficial layer with distinct chemical properties compared with the bulk material often allows for the conservation of stiffness to isolate specific chemical influences on cell behavior.[59–61,70–75] Surface patterning, in addition to the decoupling of chemical and mechanical properties, provides a promising strategy to further alter the topography of the interface in cell-biomaterial interactions.[77,78] By incorporating additional cross-linkers, relatively constant stiffness can be obtained with PEG hydrogels, demonstrating the decoupling of chemical and mechanical properties.[98,121] Copolymerizing multiple polymer units in varying ratios provides another way for decoupling by producing more than one polymer type that exhibits the same mechanical properties but different chemical compositions.[100,105–108,111,112] The copolymerization and polymer blending combinatorial library techniques enable a high-throughput approach that is utilized in elucidating cell-material relationships.[115–120] Other strategies such as using nanomaterials of different chemical compositions to achieve similar mechanical properties[100] could be considered as further alternatives to the decoupling approaches discussed here.

Although significant progress has been made, it should be understood that elucidating structure-function relationships is not easy, because decoupling two properties often results in an unexpected change of another property due to the highly interdependent nature of material properties. It should also be noted that the cellular response can also alter the material properties, effectively creating a complex feedback mechanism ("function-structure relationship") that changes in real time as the biomaterial interacts with the surrounding cells and tissues in a highly dynamic fashion.[19,122] It is, therefore, of great importance to keep improving the methods to more precisely and accurately decouple material parameters and to thoroughly verify the improvement by investigating how the strategies affect scaffold properties and cellular responses before and after decoupling. This effort will provide a broader insight into structure-function and function-structure relationships, as well as property-property relationships, thereby establishing a whole-picture view of cell-biomaterial interactions. This is an urgent task for modern biomaterial scientists and tissue engineers in order to advance the development of instructive scaffolds for tissue engineering, regenerative medicine, and drug delivery.

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Disclosure Statement

No competing financial interests exist.

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