

Recent Advances on Surface-modified Biomaterials Promoting Selective Adhesion and Directional Migration of Cells

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Abstract The surfaces and interfaces of biomaterials interact with the biological systems in multi-scale levels, and thereby influence the biological functions and comprehensive performance *in vitro* and *in vivo*. In particular, a surface promoting the selective adhesion and directional migration of desired types of cells in complex environment is extremely important in the repair and regeneration of tissues such as peripheral nerve and blood vessel, and long-term application of intracorporal devices such as intravascular implants. Therefore, surface modification of biomaterials is a facile and effective method to achieve the desired cell-biomaterials interactions. In this short review, recent advances on the surface modification of biomaterials to regulate selective cell adhesion and migration are briefly summarized. In particular, the surface properties of biomaterials are manipulated via the convenient introduction of amino groups to the ester-based polymers, the formation of polyelectrolyte multilayers, and the fabrication of topology and gradient cues, etc., followed by the association of chemical and biological signals such as collagen, heparin, hyaluronic acid, peptides and cell growth factors. The selective adhesion and directional migration of various types of cells such as endothelial cells (ECs), smooth muscle cells (SMCs), hepatocytes and Schwann cells (SCs) are achieved over the competitive counterpart cells by the use of cell-resisting substances and cell-selective motifs on gradient substrates in most cases. Recent advances on cell behaviors in three-dimensional (3D) cell-extracellular matrix (ECM)-mimicking substrates are also reviewed.

Keywords Biomaterials; Surface modification; Gradient; Cell migration; Cell selectivity

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INTRODUCTION

The biomaterials designed currently are more and more inclined to have positive and controllable interactions with surrounding cells, tissues and environments to actively participate in the processes of tissue repair and regeneration *in situ*. The tissue regeneration is a well-organized progress that different kinds of cells should be recruited at the right time to advance the processes of angiogenesis, nerve regeneration, bone repair, and cartilage regeneration, etc.^[1–3] The selective adhesion of desired types of cells on the designed biomaterial surface would be the initial challenge, followed by the directional migration of selected cells towards desired region to accelerate the proliferation, differentiation and regeneration. For examples, in the regeneration of triple-decker arterial wall of the vessel, the faster adhesion of endothelial cells (ECs) than the vessel smooth muscle cells (VSMCs) on the bio-surface is known to accelerate the endothelialization of innermost layer and keep the new tissue from thrombogenesis and restenosis.^[4] Later, VSMCs would help to form the middle layer. The fibroblasts (FIBs) are the main cells to form outmost layer of the vessel. With the

nature of migrating faster than VSMCs, FIBs might migrate into the inner two layers, leading to the formation of scars and the angiosclerosis as well as adventitia fibrosis.^[5] A surface that selectively promotes the adhesion of VSMCs rather than FIBs and guides their directional movement would contribute greatly to the vessel regeneration.^[6]

Adhesion of cells on biomaterial surface is the precondition for the subsequent migration, proliferation and differentiation, thus triggering tissue regeneration. There are extremely complex mechanisms behind this cell behavior. Briefly, the cell adhesion depends on the interaction between the diverse receptors and ligands, both of which could locate on the cell membrane surface, biomaterial surfaces and cell adhesion molecules (CAMs).^[7] CAMs are groups of transmembrane proteins on cell membrane, including mainly the cadherin, integrin, immunoglobulin superfamily (IgSF) and selectin, which promote the cell-cell adhesion as well as cell-extracellular matrix (ECM) interaction.^[8] The cells adhering to the biomaterial surface could be analogized as they are binding to a two-dimensional (2D) ECM^[9] through the mediation of CAMs. The functionalized biomaterial surfaces appeal to certain CAMs or CAMs-contained protein complexes, giving rise to the interaction between CAMs and material surfaces, thus leading to the adhesion of selected cells.

Integrin is the primary CAMs participating in cell-ECM con-

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junction. It is expressed by the cells, consisting of 2 subunits, one α -subunit and one β -subunit.^[10] So far, the identified 18 types of α -subunit and 9 types of β -subunit form 24 kinds of known integrin. Every cell would express several kinds of integrin, which could bind to different ligands in the ECM. The conjunction between integrin and the ligand in ECM shows a weak affinity, and thus usually hundreds even thousands of these conjunctions coincide. The integrin-dependent adhesion is divided into focal adhesions (FAs)^[11] and hemidesmosome (HD).^[12] FAs are protein complexes connecting the cytoskeleton of cell with the fibronectin in ECM through adaptor proteins such as talin, α -actinin and vinculin, etc. HD is usually found in the boundary of epithelial cells adhering to the basal lamina.

After adhesion, the cell migration could be triggered by biological signals derived from cells, and by chemical as well as physical cues of the substrate. The FAs plays an important role in the cell migration. The low affinity between integrin and ECM allows the fast formation and separation between the receptors and ligands, and thus continually the FAs in rear-end of cell are dissociated and the new FAs-ECM connections are shaped in the forefront of cell, promoting the cell migration.^[13]

This short review will focus on the fabrication of biomaterial surface to enhance the selective adhesion and directional migration of different types of cells. It starts with the discussion of important factors of biomaterials influencing cell adhesion and migration. The methods for achieving selective cell adhesion and directional migration are then emphasized and the outlook of this field is finally suggested.

IMPORTANT SURFACE FEATURES GOVERNING CELL ADHESION AND MIGRATION

Physicochemical Features

A surface with outstanding capability to adsorb proteins is generally advantageous for cell adhesion. While 40%–50% of protein periphery is covered by nonpolar groups, its affinity to a hydrophilic surface is relatively low due to the high energy barrier for this surface to dehydrate. Most FDA-certified synthetic polymers such as polyurethane (PU), poly(D,L)-lactide (P-(D,L)-LA), polyglycolide (PGA) and polycaprolactone (PCL) have good biocompatibility and non-cytotoxicity, but do not possess sufficient cell-affinity and cell selectivity. In this subsection, some important physicochemical features such as surface functional groups, antifouling layers, surface charge and immobilized biological molecules are discussed with respect to cell adhesion and migration.

Surface functional groups

The free amino groups could be introduced to the surface of PU, PLLA and PCL through the ammonolysis of the ester groups, providing active sites to bond other biomacromolecules.^[14–17] Under an alkaline condition, the ester groups would be aminolyzed to form the amide bonds. When diamine such as 1,6-hexanediamine is used, one of the amine groups remained free for functionalization. The glutaraldehyde (GA) is frequently used as the linker to immobilize biomolecules having amino groups. For example, Qiu *et al.*^[18] functionalized galactosylated chitosan to the PCL scaffold to improve the selective adhesion

of human hepatocellular carcinoma (HepG2) cells. Zhu *et al.*^[19] coupled collagen to poly(L-lactide) (PLLA) membrane to promote the adhesion of human umbilical vein endothelial cells (HUVECs). Zhu *et al.*^[20] further immobilized gelatin, chitosan and collagen on aminated PU to accelerate the adhesion of HUVECs. The aminated surface also establishes a foundation for the loading of polyelectrolyte multilayer membranes through the layer-by-layer (LBL) assembly of polycations and polyanions, which provides more choices to modulate cell behaviors.^[21] Chang *et al.*^[22] studied the stiffness-controlled surface through assembling soft protamine sulfate/deoxyribonucleic acid (DNA) multilayers onto a stiff substrate. The competitive adhesion of ECs over SMCs could be realized, and ECs prefer to soft matrix while SMCs prefer to stiff one.

Antifouling layers

The “grafting to” and “grafting from” technologies have been applied to accurately control the grafting density and chain length of grafted polymers, allowing the formation of a uniform layer of antifouling polymer brushes to resist the adhesion of cells. Deng *et al.*^[23] grafted poly(hydroxyethyl methacrylate) (PHEMA) from the 3-aminopropylthiethoxysilane (APTES) immobilized substrate by means of surface-initiated atom transfer radical polymerization (SI-ATRP), and demonstrated that the PHEMA thicker than 6 nm can fully prevent the adsorption of bovine serum albumin (BSA). Chernyy *et al.*^[24] fabricated a surface of poly(2-lactobionamidoethyl methacrylate) (LAMA) brushes through SI-ATRP, which shows high affinity to galactose residue and asialoglycoprotein receptors (ASGPRs) in HepG2 cells but resists other cell adhesion. Jiang *et al.*^[25] cultured induced pluripotent stem (iPS) cells on poly(di(ethylene glycol) methyl ether methacrylate) (PDEGMA) brushes-grafted surface. The thermally swollen PDEGMA brushes would release the iPS cell colony from the surface, but remains the differentiated cells because of the varied adhesion strength after differentiation. Abdellatif *et al.*^[26] developed a photoactivatable gold substrate consisting of different ratios of cyclic Arg-Gly-Asp (cRGD) to hexa(ethylene glycol) (EG₆) molecules as well as photo-cleavable poly(ethylene glycol) (PEG) chains. By controlling the irradiated area, the cells would adhere to a specified area with desired shape (Figs. 1a and 1b). This surface also served as a platform to study the migration of epithelial cell in a multicellular manner. With a suitable density of cRGD, the “leading cells” extended more lamellipodia (Fig. 1c), thus drawing the neighboring cells to migrate through cell-cell interactions and finally driving the group migration.

Surface charge

The surface charge affects the cell adhesion *via* the electrostatic interaction with proteins or related molecules. Zhang *et al.*^[27] demonstrated that the charge density regulates protein adsorption by controlling the ratio of charged microdomains on the potassium sodium niobate ceramic through laser-irradiation. The higher charge difference between the charged domain and uncharged neighbor zone greatly increases the protein adhesion, and thus affects the cell orientation and adhesion.

Immobilized biological molecules

The immobilization of biological signaling molecules such as oligopeptides, enzymes, proteins and cell growth factors on

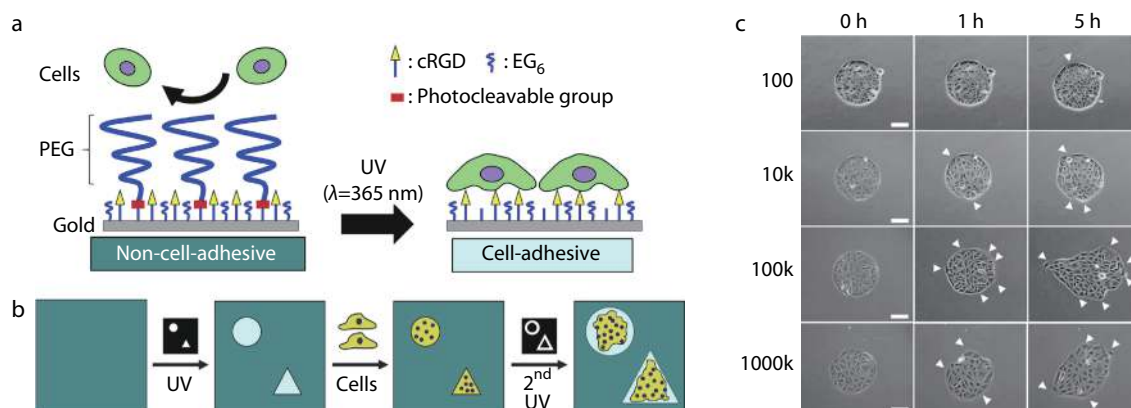


Fig. 1 (a) Substrates with tuned cRGD. (b) Protocol for the study of collective cell migration of cell clusters using precise geometry. (c) Effect of cRGD density on cluster expansion and appearance of leader cells. Arrow heads indicate leader cells. (Scale bar = 50 μm .) (Reprinted with permission from Ref. [26] Copyright (2018) Elsevier).

substrate is most feasible to achieve the selective cell adhesion.^[28] For example, Zhao *et al.*^[29] immobilized antithrombotic LTFPRIVFVLG peptide sequence (ACH₁₁) and Cys-Ala-Gly (CAG) oligopeptide to a vascular graft, obtaining a surface with multiple functions of anti-fibrinogen, anti-platelet adhesion/activation as well as higher affinity to ECs (Fig. 2). The recognition and capture of cancer cells from blood are extremely important in the diagnosis of early-stage cancers. Kaur *et al.*^[30] introduced an electrospun PCL fiber mat containing a covalently linked folic acid derivative. Because the cancerous cells can over-express the folate receptor (FR), the FR-positive HeLa cells rather than the FR-negative human embryonic kidney 293 (HEK 293) cells are selectively captured onto this mat. Song *et al.*^[31] functionalized the inner surface of a poly(methyl methacrylate) (PMMA) tube with anti-epithelial cell adhesion molecule (anti-EpCAM) antibody to effectively and selectively capture human gastric cancer (SGC7901) cells in circulating blood flow.

Gradient Cues

Following the selectively enhanced cell adhesion by means of the surface modification, much attention is paid to guide the cell migration along with an assigned direction. A surface with gradient chemical, physical and biological signals offers the opportunities to achieve directional cell migration. Two kinds of technologies have been widely used to fabricate the gradient surface. The first method is to control the reaction time of the substrate in the atom transfer radical polymerization (ATRP) reaction solution (Fig. 3a).^[32] The target surface is placed vertically in a sealed vessel, into which the reaction solution is injected gradually by a micro-infusion pump. Due to the linear relationship between the polymerization degree and reaction time in the ATRP process, the thickness of polymer brushes increases in a gradient manner along with the duration of exposure.^[32] By using this method, Li *et al.*^[33] fabricated a thermoresponsive poly(*N*-isopropylacrylamide) (PNIPAAm) surface with gradient thickness, and Ren *et al.*^[32] prepared gradient PHEMA chains. Along with the increasing polymer brush thickness, the surface turns to be hydrophilic with a better performance in anti-fouling. The other way is to prepare a solution with gradient density by means of micro-infusion pump at first. The gradient surface can be realized by immersing

the surface vertically in this reaction solution (Fig. 3b).^[34] This surface modification can be used to graft molecules and to etch the substrate in a gradient manner. For example, the poly-4-styrene sulfonate (PSS)/poly(diallyldimethylammonium chloride) (PDADMAC) multilayers^[35] were immersed in a gradient sodium chloride (NaCl) solution, forming a gradient structure. With the gradient hydration degree, SMCs tended to migrate to the direction with a decreasing hydration degree.^[34] Wu *et al.*^[36,37] fabricated a surface with gradient density of heparin, which was further transformed into gradient basic fibroblast growth factor (bFGF) density, showing a selective adhesion to VSMCs rather than ECs and MSCs. A 70% directional migration of VSMCs was observed. Besides, the gradient cues also contribute to studying the gradient process of cell differentiation. Zhu *et al.*^[38] introduced alendronate (Aln) onto the aminolyzed PCL in a gradient manner, resulting in the gradient osteogenic differentiation of bone mesenchymal stem cells (BMSCs).

Surface Topology

While the aforementioned surface modification alters cell adhesion in a 2D level, the surface topology gives the possibility to upgrade these contact interfaces into a 3D manner, which is more analogous to the ECM environment. The surface topology such as pattern, curvature and roughness, *etc.*, leads to the variation in surface energy, roughness and wettability, altering the cell adhesion and migration. The surface topology works mainly in two ways. On one hand, the topological morphology provides variable contact area for cells, suggesting that the anchoring points for cell adhesion are adjustable. The micron-sized concave regions may attract more adhered cells due to the larger specific surface area. Ma *et al.*^[39] made a honeycomb pattern with a diameter of 5.5–6.5 μm in each pore on the surface of a polystyrene film. The PSS/polyethyleneimine (PEI) multilayers were assembled on the pore. Each pore can capture one cell, and the cell proliferation can be repressed in the pores. On the other hand, the surface topology endows the surface anisotropy, resulting in regional difference in physicochemical properties. Zheng *et al.*^[40] prepared Janus PCL microparticles in 3D porous gelatin template. The coarse hemisphere is superior in adsorbing proteins, hence attracting a larger number of cells than the smooth hemisphere. By using a proper seeding

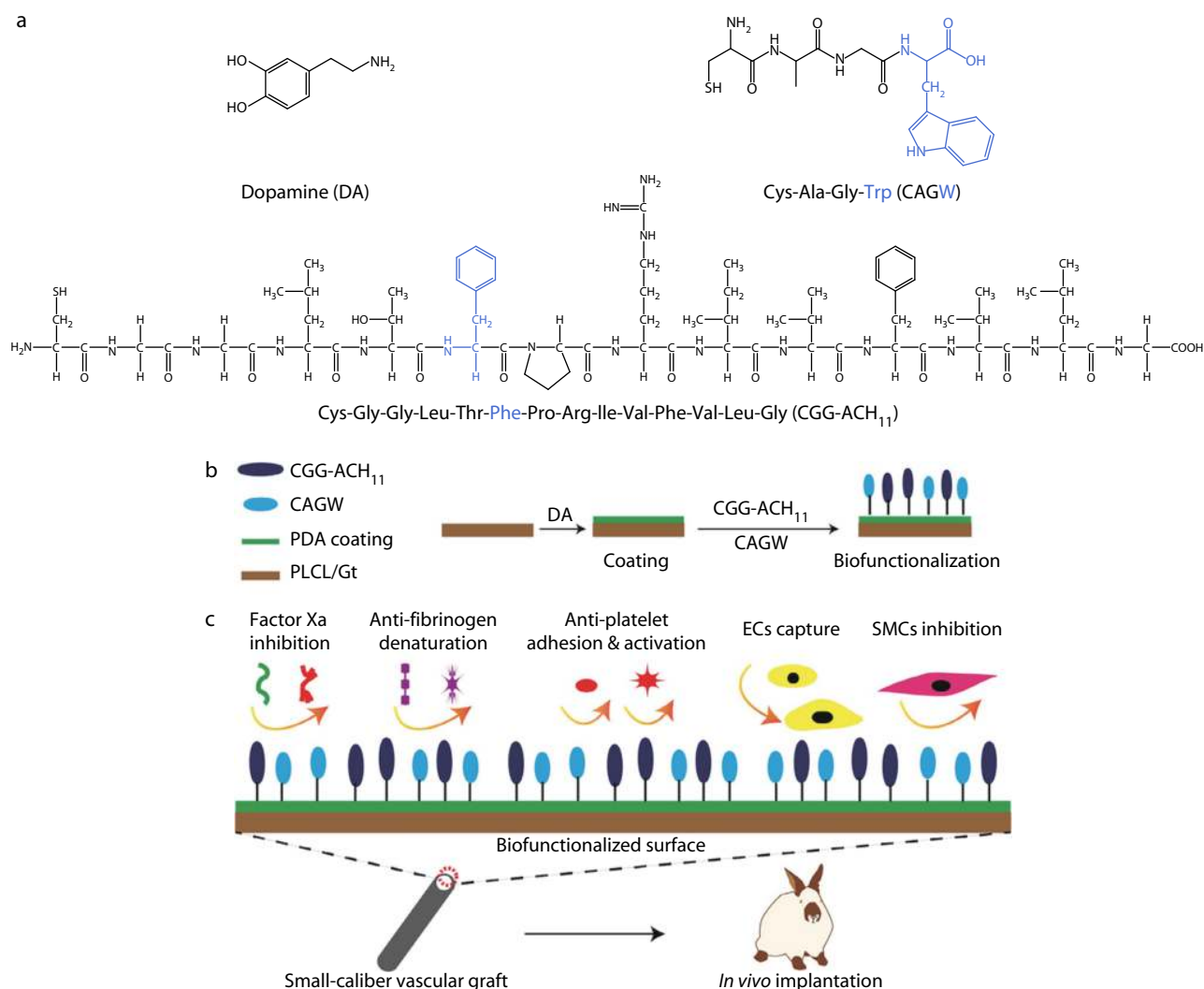


Fig. 2 (a) The structures of biofunctionalized vascular graft and (b) the preparation of multifunctional surface. (c) Multifunctional graft had anticoagulation and ECs-selective adhesion. (Reprinted with permission from Ref. [29] Copyright (2019) Elsevier).

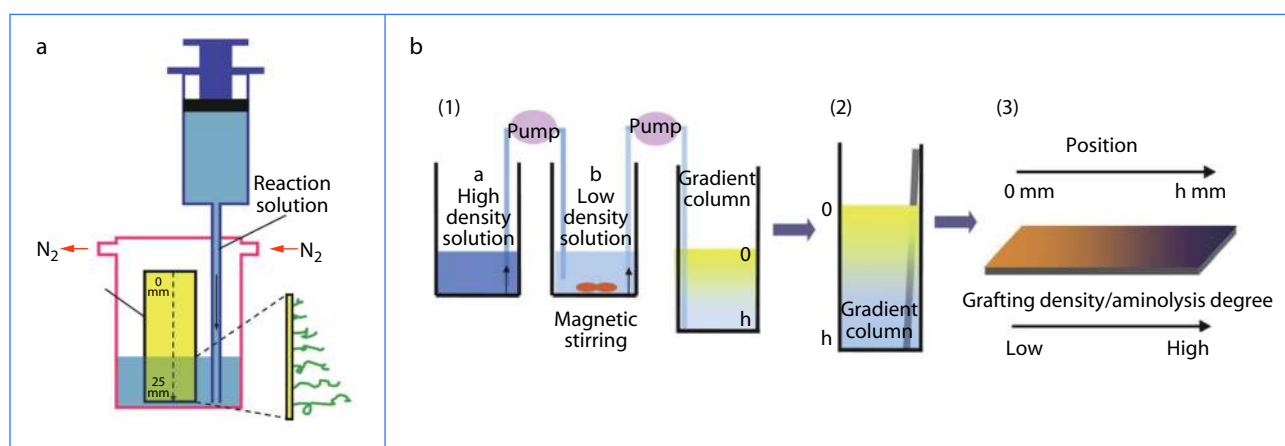


Fig. 3 (a) Schematic illustration of thickness gradient. The reaction solution is injected continuously into a container at a desired rate. Because of the different reaction time, the polymer gradient with a larger polymerization degree towards bottom side was obtained. (Reprinted with permission from Ref. [32] Copyright (2013) American Chemical Society). (b) Schematic illustration showing the fabrication of gradient solution and gradient grafting density. (1) Generation of a continuous density gradient solution. (2) Vertical incubation of the substrate into the gradient solution. (3) The obtained gradient film. (Reprinted with permission from Ref. [34] Copyright (2013) Elsevier).

protocol, fibroblasts were selectively adhered on the coarse hemisphere and ECs occupied the smooth hemisphere.

Besides modulating cell adhesion, the surface patterning structure is very effective to guide the directional cell migration because the cell can respond to anisotropic features in the environment (curvotaxis). By designing ultra-smooth sinusoidal surfaces with cell-scale curvature landscapes, the cells were observed to migrate towards the concave curvature.^[41] This migration is resulted from the intercellular force generated through the interaction between the nucleus and the cytoskeleton. Figs. 4(a)–4(d) clearly present the tropism of nucleus towards concave, and Fig. 4(e) illustrates the compression of the nucleus that induces the cell slipping into the concave, where the nucleus can stay relaxed. The linear concave-convex structure with a proper hollow space to

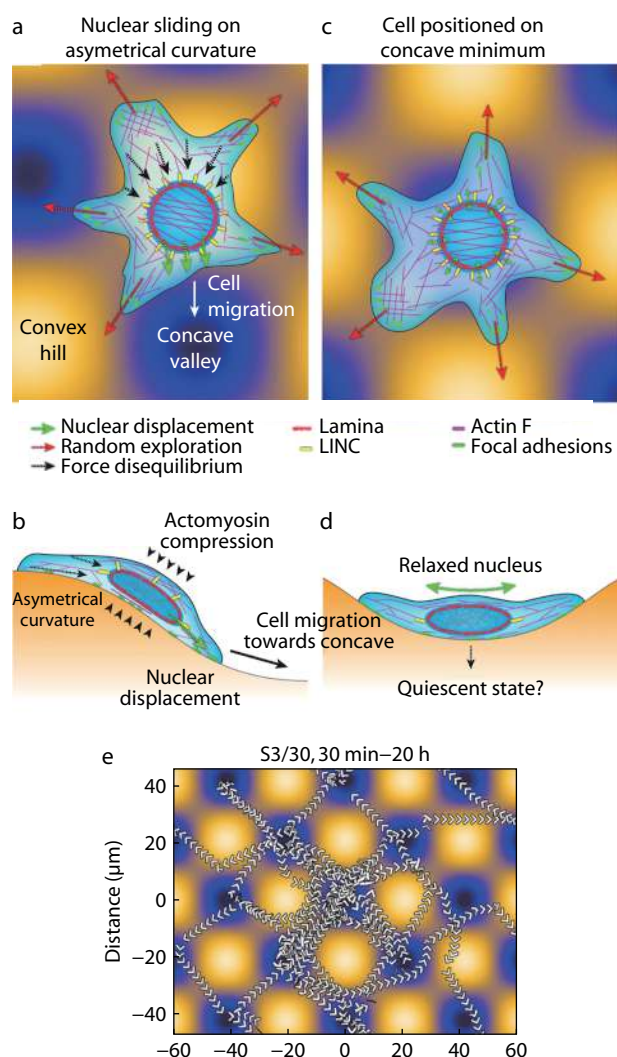


Fig. 4 Adhesion on asymmetrical curvature (a) triggers nuclear sliding toward concave, altering the random walk of the cell and leading to cell positioning on concave valley (c). (b, d) Side views showing actomyosin compression of the nucleus and its relaxation on concave curvature. (e) Curvotaxis allows adherent cells to avoid convex hills during their migration. Arrowheads indicate movement direction. (Reprinted with permission from Ref. [41] Copyright (2018) Springer Nature).

trap the cell and directional pathway for cells to migrate was also investigated. Zhang *et al.*^[42] striped the poly(L-lactide-co-caprolactone) (PLCL) thermally by a polydimethylsiloxane (PDMS) template, which was further entrapped with gelation to guide the SCs adhesion, elongation and directional migration. So far, most surface topology modification has been restricted on either the surface concave-convex structures or the simple surface energy distribution, and the integration of these parameters to maximally match the real ECM is still a huge challenge.

SURFACE DESIGN FOR SELECTIVE ADHESION AND DIRECTIONAL MIGRATION OF CELLS

Single chemical, biological or physical signal on the biomaterial surfaces has been extensively investigated to increase the cell adhesion and/or directional migration. The collaboration of these signals on one surface can achieve desired adhesion of the targeted cells and then directional migration, suggesting its significance for tissue repair and regeneration.

Gradient Antifouling Surface Coordinated with Gradient Biological Signals

While biological signals perform high affinity to specific cells, the immobilization of certain peptides, cytokines and cell growth factors contribute to the selective adhesion of preferred cells. Further, the gradient distribution of these biological signals has been proposed to guide the directional cell migration.^[43] Yu *et al.*^[44] immobilized methacrylate-functionalized hyaluronic acid (HA-MA) onto aminolyzed PCL film, which was further immobilized with Arg-Glu-Asp-Val (REDV) peptides through the click reaction between thiol (–SH) and alkenyl groups in a gradient manner (Fig. 5). ECs exhibited an enhanced adhesion and mobility on this surface, and a directional migration towards the direction of a higher REDV density, whereas the adhesion of SMCs was restricted significantly. They^[45] also fabricated another gradient Val-Ala-Pro-Gly (VAPG) peptide density surface, which was affinitive to SMCs rather than FIBs.

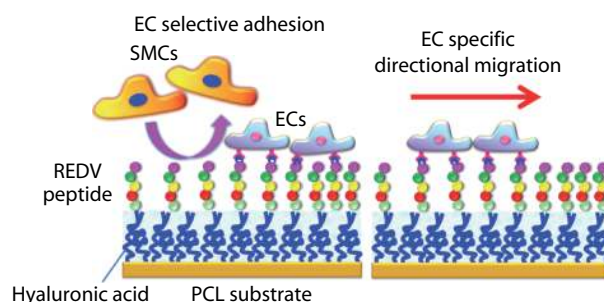


Fig. 5 Schematic illustration to show the EC-selective peptide (REDV) density gradient created on a uniform MA-HA layer, and its influence on the selective adhesion and migration of ECs over SMCs. (Reprinted with permission from Ref. [44] Copyright (2016) American Chemical Society)

By combining the continuous injection technology with the SI-ATRP, the substrate can be grafted with polymers with a controllable gradient thickness. By this way, Wu *et al.*^[46] fabricated the block polymers of poly(2-hydroxyethyl methacrylate (HEMA)-co-glycidyl methacrylate (GMA)) and

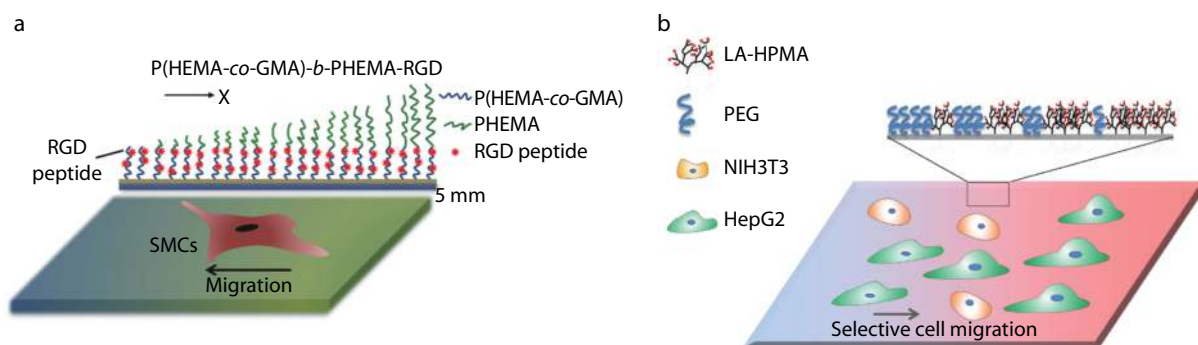


Fig. 6 (a) Schematic illustration to show the structure of depth localization gradient of RGD peptides and its mediation of directional cell migration. (Reprinted with permission from Ref. [46] Copyright (2018) Elsevier); (b) The influence of complementary gradient of LA-HPMA and PEG surface on the mobility of HepG2 and NIH3T3 cells. (Reprinted with permission from Ref. [47] Copyright (2017) Elsevier).

used as the base flat layer for the top PHEMA gradient (Fig. 6a). The Arg-Gly-Asp (RGD) peptides were immobilized through the ring-opening reaction of the epoxy group of GMA. Even though the anti-fouling PHEMA and cell-affinitive RGD frequently present opposite effects to the cell adhesion, this gradient surface reveals an appropriate interplay to guide the continuous change of cell density. Meanwhile, the cultured SMCs migrate towards the direction of thinner PHEMA region.

The surface can also be functionalized with complementary density gradients, on which two different gradient signals were concurrent in the opposite directions. Liang *et al.*^[47] prepared a type of complimentary gradients by immersing a dopamine-coated glass substrate into PEG gradient solution and subsequently into a galactose-modified hyperbranched polymers (LA-HPMA) solution (Fig. 6b). The affinity of LA-HPMA to the HepG2 and anti-fouling ability of PEG increases the selectivity of the surface, and the gradient distribution of LA-HPMA raises the probability of the directional migration of HepG2 cells.

Topologic Surface Coordinated with Biological Signals

The topologic surface shows a well-known phenomenon of contact-guidance effect to cells, leading to the alignment of cells along the features such as grooves and ridges.^[48] The introduction of biological signals onto this surface is further studied to achieve a better directional migration of cells. Zhang *et al.*^[49] molded a groove-ridge structure on maleimide-functionalized PLLA film, which was further clicked with the thiol-terminated CQAASIKVAK peptides derived from laminin. SCs adhered more easily on this surface with an aligned morphology, resulting in a faster and better directional migration.

Cell Migration in ECM Mimicking 2D and 3D Environment

Most of the aforementioned surface design is still difficult for practical use due to the complex mechanism beside the cell behaviors. By contrast, a designed biomaterial surface with ECM-mimicking properties would greatly demonstrate the true response of cells towards external stimuli. The interaction between ECM glycopeptides and cell surface marker plays an important role in cell migration, but its mechanism is difficult to track. Sangabathuni *et al.*^[50] put forward a platform

to study the combinatorial libraries of ECM glycopeptides by introducing the host-guest strategy. β -Cyclodextrin-functionalized glycopeptides were conjugated to adamantine-appended collagen that can adhere onto cell surface and expose the glycopeptides, whose effect on the ECM, furthermore on the cell migration preference could be fully investigated without the interference of other glycopeptides. Wang *et al.*^[51] fabricated elastomer pillar arrays using the PDMS, whose modulus could be controlled by changing the pillar height. The modulus was 4.6 and 53.68 kPa when the height was 9 and 4 μ m, respectively. These pillars were arranged into height gradient arrays. Cells migrated towards the harder substrate with lower pillar height. This tropism appeared not only on a linear gradient but also on a circular state. The formation of focal adhesion on a soft 3D substrate is more difficult than that on a 2D hard substrate. Elkhatib *et al.*^[52] demonstrated another cell adhesion mode dominated by the tubular clathrin/adaptor protein 2 (AP-2) lattices, which is more critical in a 3D ECM environment. It forms a tubular structure to pinch the collagen, providing more anchoring points between the collagen fiber and the cell surface, thus participating in focal adhesion and promoting cell migration along with the fiber. Cheng *et al.*^[53] fabricated the curved wave topography on poly(ethylene terephthalate) (PET) surface using Direct Laser Writing (DLW), which provides more flexible and controllable method for the 3D surface modification. Hernandez *et al.*^[54] developed an *in situ* imprinting strategy to change the substrate topology such as rings and grooves surrounding a cell without extra harms to this cell by radiating the fixed points of photo-crosslinked protein hydrogel, leading to the local shrinkage of the hydrogel surface. In this way, the real-time stress of cell to the substrate stimulus could be studied. Zhang *et al.*^[55] fabricated a graphene oxide (GO)-modified miropatterned PLCL film, which was further curled to form a 3D conduit for the study of *in vivo* peripheral nerve regeneration. This surface integrated 3D surface, cell adhesion, directed group migration, desired cell differentiation as well as favorable *in vivo* nerve regeneration, laying a solid foundation for the biomaterial surface development.

SUMMARY AND PERSPECTIVES

The precise selection of cells to adhere on designed surface and the guidance of these cells to migrate along with specified

direction would largely increase the functionality of biomaterials, thus enhancing the efficiency of tissue regeneration. This short review focuses on the fabrication of surfaces to promote selective adhesion and directional migration of cells. The modification methods include change of surface compositions, and introduction of bio-signals, surface topology molding and gradient structure. Besides, the multiple applications of these methods are also summarized. In particular, the complementary gradients achieve the selective adhesion of cells and enhance their directional migration simultaneously. These studies have shown their great promise in the experiments *in vitro*. The deliberately designed surfaces are expected to meet the challenges of the complex microenvironment and thereby to show high efficiency *in vivo*.

Even though the fabrication of biomaterial surface for the selective adhesion and directional migration of specific cells has been widely investigated, the practical applications of these surfaces *in vivo* are still largely limited due to the complex microenvironment. After the implantation of biomaterials, the surgical wound would suffer from inflammation, bacterial infection and recruitment of suitable cells for tissue regeneration. A surface with multiple functions in particular stimuli-response or self-adaptivity to the variation of pH, temperature and/or reactive oxygen species (ROS) is thus very appealing. For example, in the early stage after implantation, a surface with antibacterial and anti-inflammatory properties is favorable.^[56] In the later process of tissue regeneration, various types of cells are required to perform their diverse functions: the recruitment of ECs and VSMCs to enhance angiogenesis,^[57] the collection of tissue repair cells such as osteoblasts for the osteogenic differentiation,^[58] and the supply of SCs and FIBs to increase the generation of nerve. The triggers of these response could be pH,^[59] temperature,^[60] ROS,^[61] enzymes,^[62] ultraviolet (UV)^[63] and magnetic field.^[64] Therefore, a surface that can respond to multiple signals in a respective time scale and magnitude would be more desirable.

Another key issue that should be emphasized is the degradation of the modified surface under *in vivo* environment, especially the implantation of stimuli-responsive surfaces for a long term. In such a case, it is difficult to predict whether the elaborately designed surface could still play the role in controlling cell behaviors. In some other cases, the stimuli-responsive degradation can be used to design an adaptive surface to achieve specific functions that are difficult to realize by other methods. A recent elegant study has shown that the thrombin-triggered degradation of surface-coating can release hemolytic agent to decompose the formed thrombus, whereas the remained antifouling layer can persistently prevent the adhesion of platelets.^[65] In summary, the design concept for future biomaterial surfaces would be more diversified and comprehensive, so that both the cell behaviors and lifetime of the designed surfaces should be mutually combined.

BIOGRAPHY

Chang-You Gao received his Bachelor degree (1990), Master degree (1993) and Ph.D of Polymer Chemistry and Physics (1996) from Jilin University. He worked in Department of Polymer Science and Engineering of Zhejiang University as a

postdoctor associate (1996–1998). He was appointed as an associate Professor at 1998 and a full Professor at 2001. He was elected as a fellow of the international federation of biomaterial science and engineering societies (2016), and a fellow of the American academy of medicine and biological engineering (2017). He leads a lab focusing on biomedical polymers for tissue repair and regeneration since 1996.

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