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Fabrication of micro-nano patterned materials mimicking the topological structure of extracellular matrix for biomedical applications

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ABSTRACT

With the advent of tissue engineering and biomedicine, the creation of extracellular matrix (ECM) biomaterials for *in vitro* applications has become a prominent and promising strategy. These ECM materials provide physical, biochemical, and mechanical properties that guide cellular behaviors, such as proliferation, differentiation, migration, and apoptosis. Because micro- and nano-patterned materials have a unique surface topology and low energy replication process that directly affect cellular biological behaviors at the interface, the fabrication of micro-nano pattern biomaterials and the regulation of surface physical and chemical properties are of great significance in the fields of cell regulation, tissue engineering, and regenerative medicine. Herein, we provide a comprehensive review of the progress in the fabrication and application of patterned materials based on the coupling of mechanical action at the micro- and nano-meter scale, including photolithography, micro-contact printing, electron beam lithography, electrospinning, and 3D printing technology. Furthermore, a summary of the fabrication process, underlying principles, as well as the advantages and disadvantages of various technologies are reviewed. We also discuss the influence of material properties on the fabrication of micro- and nano-patterns.

KEYWORDS

micro/nano hybrid materials, patterning fabrication techniques, extracellular matrix, substrate-cell interaction, biomedical engineering

1 Introduction

As the basic unit of biological structure and function, cells maintain the normal physiologic function and metabolism under the influence of multiple factors, such as physics, chemistry, and biology in the surrounding microenvironment, resulting in a series of life behaviors, such as growth, division, proliferation, and differentiation [1–3], and the in-depth research and exploration of cell behavior have become the key to prevention and treatment of diseases. The cellular microenvironment is composed of extracellular matrix (ECM), adjacent cells, cytokines, soluble growth factors, and receptors (Fig. 1(a)) [4]. Cells sense the ECM and make corresponding responses. The ECM is a complex hierarchical network of macromolecules, such as collagen, elastin, microfibrillar protein, and proteoglycans [5–7]. As a dynamic and versatile chamber, the ECM supports cell adhesion, and differentiation, as well as tissue development, function, and repair by regulating the production, degradation, and remodeling of ECM components [8–10]. Due to the structural, biochemical, and functional diversity of the components, the ECM is endowed with special physical, biochemical, and biomechanical properties, such as physical stiffness, porosity, surface topology, and morphology, which affect cell division, migration, and polarization and other related biological behaviors and functions [11–13], among which the stiffness of the ECM is the basic attribute by which cells sense external forces and respond to the environment in an appropriate way [14, 15]. Similarly, cells sense and respond to intrinsic mechanical properties of the ECM by exerting traction through intracellular contraction mechanisms (Fig. 1(b)). In a less stiff matrix, the cell pulls the matrix towards the cell, while in a harder matrix, the forces generated by cells can lead to local adhesions and the formation of stressed fibers [16, 17]. For example, the ECM can negatively affect cell migration, differentiation, and proliferation during the hardening or aging in disease states, such as cancer and fibrosis [18–20]. Moreover, the extracellular matrix composed of abundant polysaccharides and fibrin is a dynamically changing structure, and ECM components not only provide dynamic tissue integrity, but also drive different biological responses as signaling molecules to regulate cell fate and tissue regeneration *in vivo*. From the perspective of biochemistry, ECM dynamically exhibits indirect signaling properties (Fig. 1(c)), which could interact with cells indirectly by binding to cell surface receptors or through growth factor presentation [21]. For example, integrins are a type of transmembrane receptors that connect the extracellular environment with the cytoskeleton and mediate cell migration, proliferation, and differentiation [22, 23]. Different types of integrins participate in the direct binding to ECM components or other cell surface adhesion molecules and receptors [24], and the ECM enhances extracellular regulated

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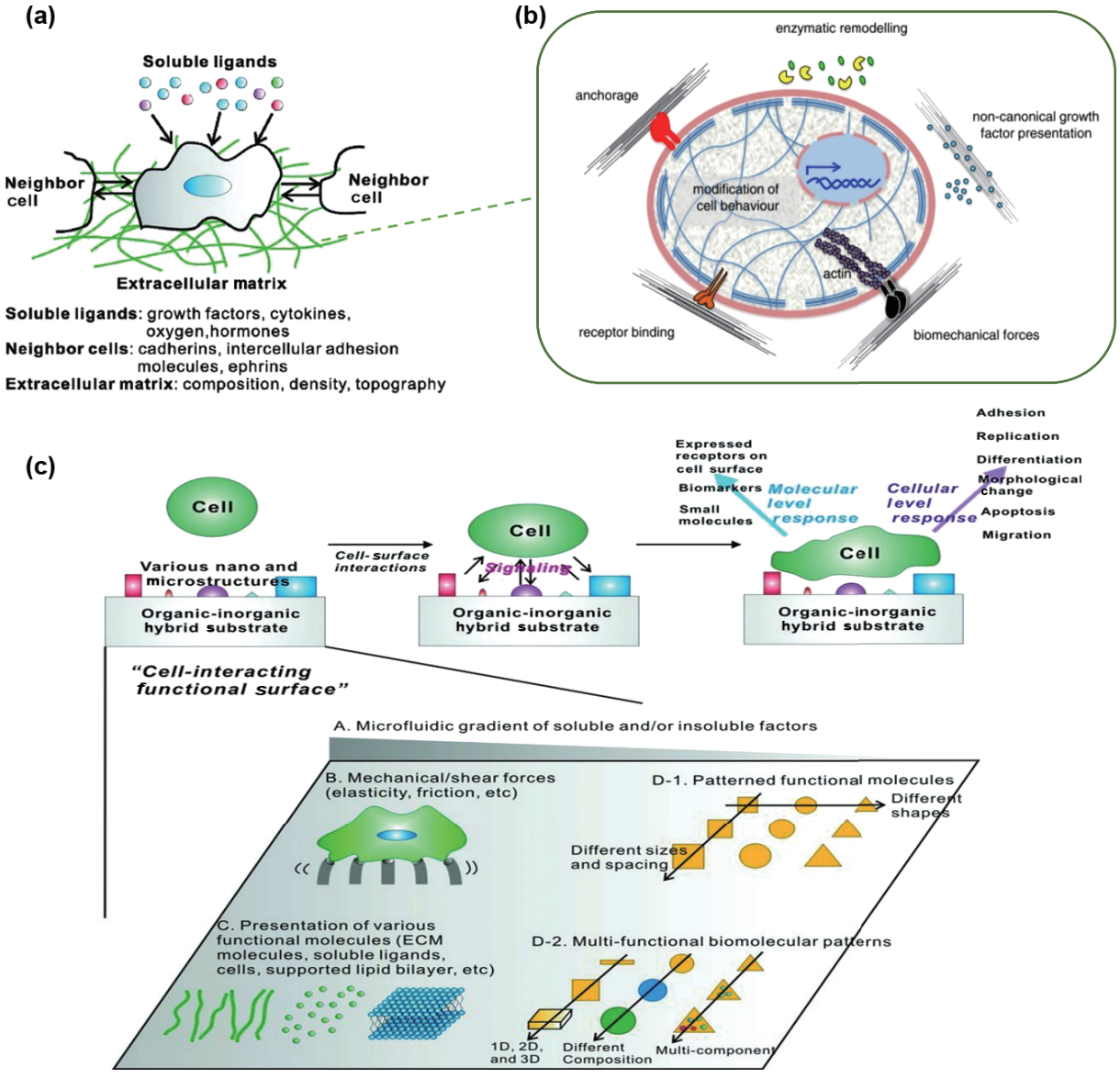

Figure 1 The substrate-cell interaction. (a) The schematic representation of the complex cellular microenvironment, including extracellular matrix, cells and soluble ligands. Reproduced with permission from Ref. [63], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2010. (b) The role of extracellular matrix in the regulation of cell behavior. The ECM can directly bind different types of cell surface receptors or co-receptors to mediate cell anchorage and act by non-canonical growth factor to regulate cell behavior. Reproduced with permission from Ref. [64], © Published by Elsevier B.V. 2014. (c) A schematic illustration of combinatorial cellular microenvironment integrated with bio-nanoengineered functional surface interfaces. Using various micro and nano patterning techniques to control the material's features, shape, spacing, and composition to create biological nanoarrays with multiple functional and structural types, including 1D, 2D, and 3D bio-nanoarrays (arrays of proteins, lipids, nucleic acids, etc). Reproduced with permission from Ref. [63], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2010.

protein kinases (ERK) activity by aggregating integrins, thereby enhancing cell contraction produced by Rho GTPase (Rho)/Rho-associated kinases (ROCK) to promote tumor occurrence [25]. The structure of ECM will change dynamically with time, including composition change, biomacromolecule network reorganization and enzyme-mediated degradation, resulting in ECM development and remodeling. Studies have shown that reducing dynamically extracellular stiffness upregulates transforming growth factor-beta (TGF-β) to induce apoptosis, while increasing dynamically stiffness causes metastasis of epithelial stroma and regulates the PI3K/Akt (phosphatidylinositol 3-kinase/ protein kinase B) signaling pathway [26]. The downstream signaling pathway is directly activated by local focal adhesion kinase (FAK) or PI3K, thereby dynamically regulating self-renewal and proliferation of cells [27, 28], and achieving an interaction between the ECM and cells. Therefore, research simulating the ECM has a great prospect in the field of biomedicine and has a wide range of applications in tissue engineering, biomaterials, and regenerative medicine.

The dynamic interaction between cell membrane receptors and active ligands in ECM is key to the occurrence of various cellular behaviors, physiological and pathological processes and the key to the fabrication of bioinspired structures. Therefore, the ideal biomaterials should have the dynamic properties of natural ECM, such as cell-mediated dynamic ECM remodeling, the dynamic relationship between physical and biochemical signals in microenvironment to guide the direction of cell fate, and the regulation of dynamic cytoskeleton to affect the formation and morphology of mesenchymal stem cell (MSC) cartilage [29–33], thus playing an important role in tissue engineering. Biomimetic dynamic micro/nano structures, including micro/nano patterns [34, 35], micro/nano fibers [36, 37] and porous scaffolds [38, 39], undergoing morphological changes and biochemical reactions with certain external stimuli. These dynamically tunable memory patterns have great influence on cell behavior *in vitro*, and could provide important applications for mediating cell fate and tissue

engineering. More than ten years ago, Tsuda et al. integrated two thermosensitive polymers with different critical temperatures on the same substrate by hollow template method to obtain a patterned dual thermosensitive cell culture surface [40, 41]. This system dynamically controlled the hydrophobicity/hydrophilicity of the surface, and realized the patterned co-culture of two kinds of cells by using the selective dynamic adhesion of hematopoietic cells (HCs) and endothelial cells (ECs). Implantation of dynamic porous micro-nano fiber scaffold through minimally invasive surgery could regulate and promote cell survival [42]. In addition, Zhang et al. grafted poly(N-isopropylacrylamide) (PNIPAM) onto shape-memory polymers (SMPs) column, and realized precise control of wettability and cell regulation by dynamically controlling of microstructure and surface chemistry [43]. In addition to regulating cell fate, dynamic micro/nano patterns are applied in tissue engineering. Zhao et al. prepared a memory electrospun nanofiber membrane of polycaprolactone/gelatin methacrylate by electrospinning technology [44], which can switch from temporary planar shape to initial tubular shape when the external temperature increases from room temperature to physiological temperature. The membrane with dynamic patterned micropores is applied to the treatment of bone defects. New bone growth can be applied by dynamically regulating the shape of the patterned membrane [33]. In addition, Liu et al. implanted artificial tubular polymer stents with dynamic, biologically unpaired micropatter surfaces into carotid arteries of New Zealand white rabbits to effectively capture endothelial progenitor cell, smooth muscle cells and endothelial cells in blood [45]. A homogeneous vascular tissue with excellent anticoagulant activity is formed and has mechanical properties similar to those of natural blood vessels. Therefore, biomimetic dynamic micro/nano patterns of the ECM that dynamically change the morphological or chemical structure and combine bioactive molecules could realize the application in the fields of regulating cell fate, tissue engineering and other biomedical applications.

The micro-nano pattern topology with a specific geometry is widely present in organisms, thus endowing organisms with unique biological functions [46, 47]. Due to the special topological arrangement and high yield, micro-nano pattern materials are widely used in biological interface substrates [48–53]. Micro- and nano-patterned materials, with the special optical, electrical, and chemical properties due to the periodic arrangement of building blocks, have been widely used in biomedical fields, such as optoelectronic devices, microfluidic devices, and biological and chemical sensors (Figs. 3(i) and 3(j)) [54–60]. Micro-nano pattern materials generally refer to materials with patterned interfaces with a periodic arranged in the nanometer-to-micron size level [61, 62]. Physical properties, such as topology, stiffness, stress, and strain of the ECM, are important factors for regulating physiologic and pathologic processes, including cell growth, proliferation, differentiation, and apoptosis. Therefore, constructing micro-nano pattern materials that mimic the topological structures and stress tendencies of the ECM, as well as stiffness distribution, provides cells with anchoring points and topological growth environments. Through surface modification, these materials transmit dynamic biomechanical and related biochemical signals, which in turn regulate cell orientation, migration, differentiation behavior, and tissue engineering. Currently, the fabrication technology of micro-nano pattern materials is a core issue in material science, with great theoretical and practical significance. Herein, we have reviewed how a range of technologies, including lithography, micro-contact printing, electron beam lithography, electrospinning, and 3D printing technologies, enable construction of pattern materials based on ECM micro- and nano-scale morphology coupling mechanical action, and summarize recent research progress in biomedicine. We also described the latest impressive applications, the synthesis process, and principles of the micro-nano pattern materials in biomedicine, as well as the advantages and disadvantages of various technologies. Finally, we discussed the influence of material properties on the fabrication of micro-nano patterns.

2 Development and applications of micro-nano pattern materials mimicking ECM in biomedicine

As tissue engineering and biomedicine continue to advance, micro-nano pattern materials that simulate ECM have gradually been applied because these materials influence cell behaviors, such as proliferation, differentiation, migration, and apoptosis. At the beginning of the last century, by observing that spider webs could affect cell behaviors, Harrison et al. proposed the innovative concept that the substrate can direct cell contact, which was inspired by the observation that a spider's web influences cell behavior [65]. Cells on micro-nano patterns independently exhibit behavior changes, such as orientation alteration, migration, division, and reorganization of the cytoskeleton, in addition to the physical and biochemical factors present in the topological structure. In 1997, Whitesides and Ingber published an article in "*Science*" that showed pattern shape and size affects cell biology expression [66]. This finding marked the beginning of proper pattern technology application in biomedicine. At the beginning of this century, Teixeira et al. constructed silicon oxide groove structures that were comparable to ECM structure and scale, and successfully induced the migration and longitudinal elongation of human corneal epithelial cells, proving that *in vitro*-simulated ECM structures significantly impact cell physiologic behavior [67]. Additionally, Grevesse and Polacheck reported that the stiffness gradient range of substrates *in vitro* (50–2000 pa) was critical in guiding cell differentiation and migration [68, 69]. It was further reported that a pore size and density gradient in ECM *in vitro*, as well as gradients in the concentration of surrounding cells, induced a range of biological phenomena, such as morphogenesis, chemotaxis, and wound healing [70, 71]. Growth and soluble factors in adipocytes combine with the ECM in tissues. Therefore, micro-nano processing technology can bind soluble factors to the surface of biological materials through cell-mediated proteolysis or external physical stimulation. In recent years, a wide range of construction techniques have been used to prepare micro-nano pattern materials for research involving biomedicine application, such as regulation of cell behavior and the interaction between cells and materials. The next section describes micro-nano pattern material preparation and fabrication technology.

3 Preparation and fabrication techniques of micro-nano pattern materials

Micro- and nano-patterning technology combines micro- and nano-fabrication, micro-processing, electrochemistry, photochemistry, and surface chemistry to create and construct physical, chemical, and biological parameters related to cells [72–76], ultimately using various etching and modification techniques to build micro- or nano-scale patterned materials. Currently, micro- and nano-patterning technology can be mainly categorized into three types of construction principles: "top-down", "bottom-up", and a combination of both [77–79]. "Top-down" technology refers to removal of some substances on the material surface according to specific processes, such as etching, molding, and deposition, to achieve dimensions in the micro- or nano-scale (Figs. 3(g) and 3(h)), including photolithography,

electron beam etching, and nanoimprinting technology. "Bottom-up" technology involves using microscopic building blocks as basic units, arranging the building blocks in a specific pattern to form micro- and nano-patterned materials, including colloidal etching, block copolymer etching, and 3D printing technologies. The combination of "top-down" and "bottom-up" techniques results in patterned materials with special micro-nano structures. These micro-characteristics structures could effectively guide and control cell growth behavior, make cells present specific arrangements and functions, and even restrict cells in limited spatial positions, which are widely used in the fields of cell biology, drug screening and tissue engineering.

3.1 Photolithography technology

The photolithography technique, which originated from the semiconductor industry, utilizes the principle of photochemical reactions, and physical and chemical etching to transfer the target patterns on the template to a fixed material. UV light is used to irradiate and expose the material surface coated with photoresist, followed by development to obtain the desired geometric patterns. This technique is currently the most widely used microscale patterning method [80–82]. Typically, solid materials are first spin-coated with photoresist and pre-baked, followed by UV exposure of the coated substrate. After exposure and development, the pattern on the template is successfully transferred to the solid substrate, and surface-modified materials, such as proteins, are subsequently adsorbed to facilitate cell adhesion and growth (Fig. 2(g)) [83]. Micro- and nanoscale patterned materials fabricated by photolithography can precisely manipulate and control cells to determine the interactions between cells and patterned interfaces (Figs. 2(a) and 2(b)) [84–86]. Klein and Striebel designed and processed a series of spider-web-like structures that undergo reversible deformation under single-cell force using photolithography with photoresist [87]. By mimicking the 3D contact point distribution between extracellular matrix and cells, controllable cell-matrix contact point distribution and adjustable hardness scaffolds were constructed. These scaffolds provide reference for researching the effects of the three-dimensional structure and elasticity of bionic extracellular matrix on single cell differentiation and tissue formation through the rhythmic deformation of single myocardial cell. Xu et al. used photolithography to imprint specific structures on a complementary polydimethylsiloxane (PDMS) template with a silicon wafer substrate to construct a 3D hydrogel substrate with a specific structural array [88]. By mimicking extracellular matrix topology, they developed 3D *in vitro* cell culture system with living cell culture array to explore the application of microfluidic cell culture system in high-throughput drug screening. Japanese scientists used photolithography with photo- and cross-linkable poly vinyl alcohol (PVA) to form micro-patterned surfaces to control and regenerate cell morphology, effectively guiding and controlling cell growth behavior through micro-patterned materials with good biocompatibility [100]. As a stable and mass-producible method, photolithography is a relatively universal and mature means of constructing micro- and nano-scale patterned materials for regulating cell behavior. Currently, the resolution can achieve preparation of structures ranging from several micrometers to 100 nm. However, the complex and time-consuming process, and the use of chemical solvents and photoresists that are prone to contamination and toxicity, remain limitations for widespread application in the field of biology. In addition, defects, such as diffraction from radiation sources, also make it difficult to control costs [90].

3.2 Soft lithography technology

Soft lithography technology is a new type of micro-nano pattern replication technology that transfers a special pattern onto a substrate material through a stamp with engraved graphics using technology, such as printing, molding, and embossing, also known as soft printing [91]. Typically, the pattern is first etched onto a silicon wafer, after which the wafer is spin-coated with a polymer, such as PDMS, and a curing agent to create a micro-nano pattern material. Traditional micro-contact printing and developed nano-imprint lithography technologies are currently the main methods for the preparation of micro-nano pattern materials using soft lithography technology. Because soft lithography can be used to construct three-dimensional and curved microstructures while also precisely regulate surface chemical composition, it has demonstrated enormous potential for application in fields, such as cell biology, microfluidics, chip laboratories, and flexible optoelectronic devices.

3.2.1 *Micro-contact printing technology*

As a type of soft lithography technology, micro-contact printing technology is an effective method for preparing micro-nano pattern materials over large areas [92]. This process involves spreading the required "ink" on the surface of a stamp, followed by pressing the ink-coated stamp onto the surface of a new substrate that needs to transfer the pattern. The surface of the substrate captures the ink molecules through van der Waals interactions with the ink molecules, thus creating micro-nano patterns (Fig. 2(h)). Micro-contact printing is a low cost, large area method for creating high quality pattern surfaces [93, 94]. Lee and Abdeen used micro-contact printing technology and micro-indentation methods to construct an array of circular micro-holes on soft PDMS and expedite the differentiation of mesenchymal stem cells [95]. By simulating the dynamic changes in the composition of adhesion ligands when the extracellular matrix contacted with cells, the optimal microenvironment for controlling stem cell differentiation into these "soft" lineages without using medium supplements was revealed. Zheng et al. constructed a base structure of grooves and elastic membranes using micro-contact printing and photolithography to simulate the survival bases of blood cells and the flow environment of blood vessels [96]. They found that the arrangement of cell stress fibers changed dynamically with cell type and stimulation type, which proved that flow stretch chip was a reliable tool to simulate the extracellular matrix of blood cells *in vivo*. Micro-contact printing technology can also be used to produce patterned surfaces with anti-adhesive fibronectin to simulate extracellular matrix, which can control the spatial distribution of the extracellular matrix and the direction of cell polarization [97, 98]. Micro-contact printing technology is convenient to operate, low cost, and less-demanding substrate materials, thus micro-contact printing technology has been widely applied in industries, such as bio-medicine. The resolution of directly prepared polymer surface patterns using micro-contact printing methods is often reduced by the large size or multiple polymer co-valences.

3.2.2 *Nano-imprint lithography technology*

Nano-imprint lithography technology developed on the basis of soft lithography technology, using rigid molds instead of elastic polymer stamps (Figs. 2(d) and 2(e)). Typically, organic polymer materials are coated on the mold, and after the imprint material uniformly fills the mold surface, the mold is pressed onto a flat substrate to create micro-nano patterns (Fig. 3(a)). Charest and Eliason used micro-imprint methods to process vertical stripe substrates similar to extracellular matrix on groove surfaces for regulating osteoblast alignment cultivation, and constructed different pattern materials for biomedical research [103–105]. Zhang et al. constructed stripe nano-graphene micro-patterns

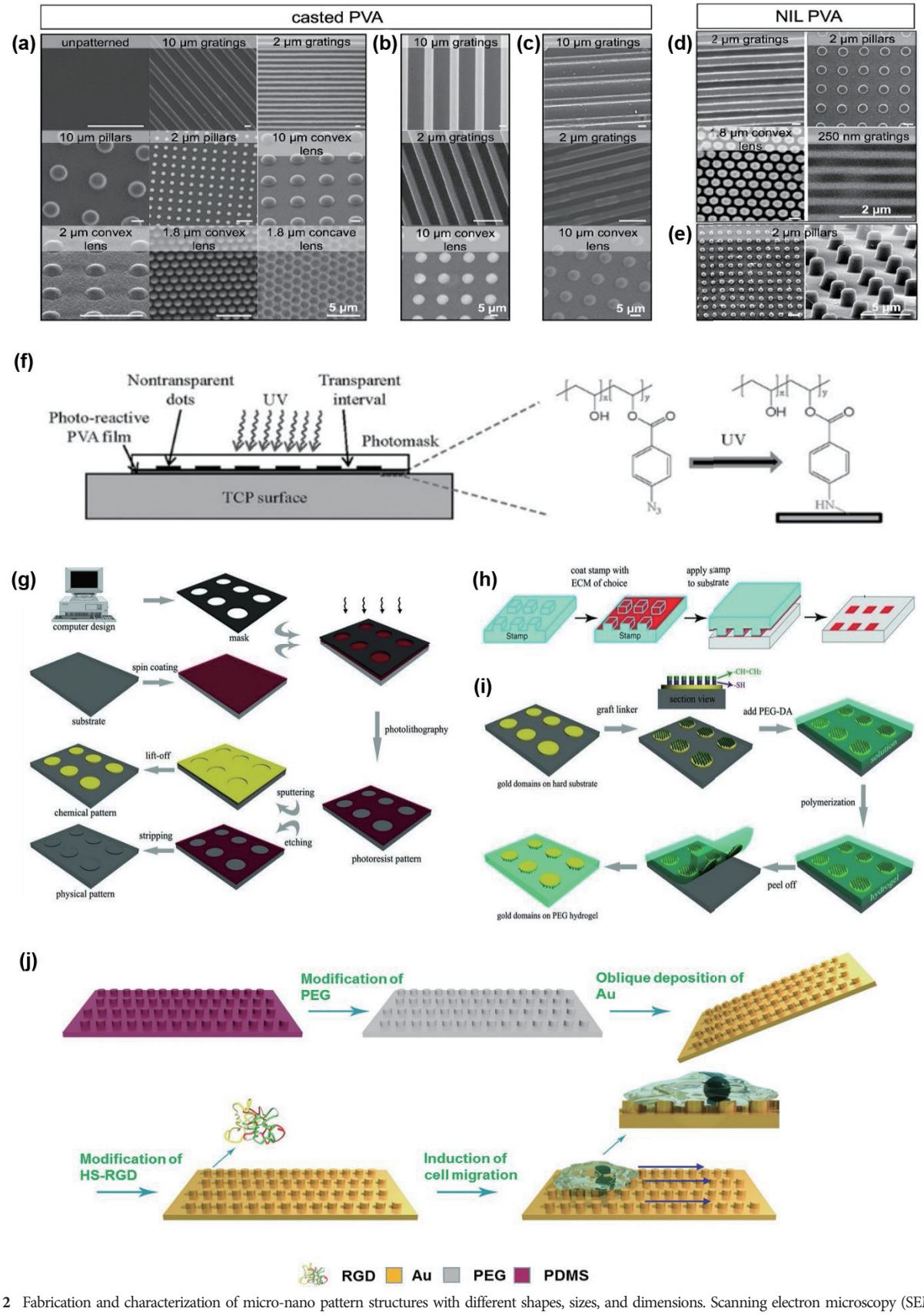

Figure 2 Fabrication and characterization of micro-nano pattern structures with different shapes, sizes, and dimensions. Scanning electron microscopy (SEM) and environmental SEM (ESEM) images of PVA micropatterned films with various topography via ((a)–(c)) casting and ((d) and (e)) nanoimprint lithography. Reproduced with permission from Ref. [99], © Elsevier Ltd. All rights reserved 2016. (f) PVA micropatterning was performed using lithography to culture cells. Reproduced with permission from Ref. [100], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2016. (g) Main steps and operations of photolithography to fabricate topography patterns. Reproduced with permission from Ref. [91], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2013. (h) Microcontact printing to fabricate chemical patterns. Reproduced with permission from Ref. [101], © Elsevier Ltd. All rights reserved 2010. (i) Using lithography to generate a gold micropattern on a polyethylene glycol (PEG) hydrogel. Reproduced with permission from Ref. [91], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2013. (j) Arrays of PEG/RGD anisotropic PDMS columns were fabricated using lithography. Reproduced with permission from Ref. [102], © Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim 2019.

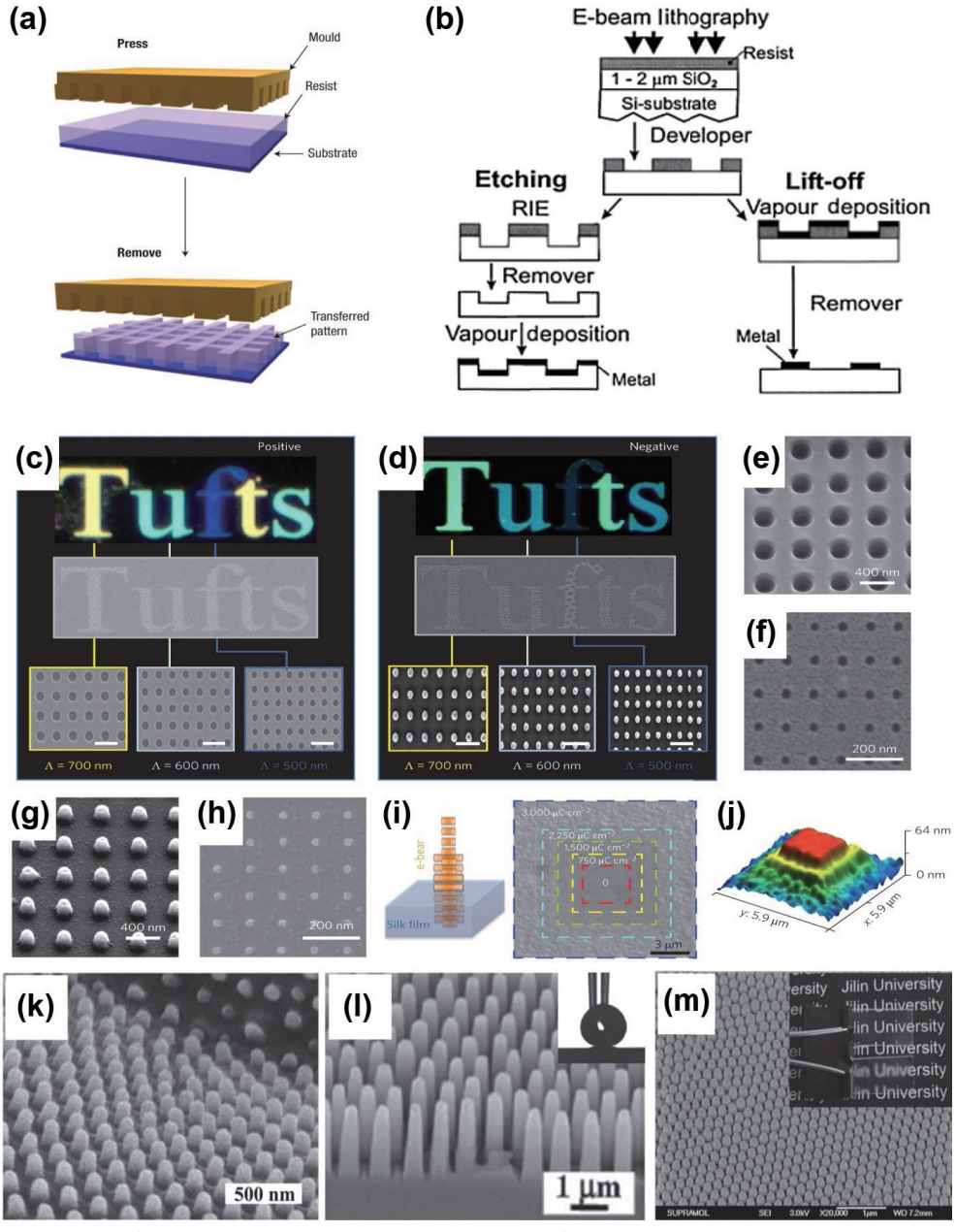

Figure 3 Three different methods to fabricate mirco/nano pattern materials. (a) Schematic of the nanoimprinting technique. Reproduced with permission from Ref. [90], © Springer Nature Limited 1969. (b) Schemes for two fabrication strategies for surface-enhanced Raman scatting (SERS) substrates using electron-beam lithography. The left side process consists in a chemical etching that follows the electron beam exposing, the dissolution of the remaining PMMA layer and deposition of metal. The right side shows a metal deposition immediately after the e-beam exposition. After removal of the photoresistor layer, the substrate will present a series of isolated nano particles. Reproduced with permission from Ref. [123], © Elsevier Science S.A. All rights reserved 1998. Using electron-beam lithography to generate silk nanostructures on (c) positive and (d) negative resist. (e)–(h) SEM images of mirco/nano pattern materials and structure diameter is 30 nm. (i) Three-dimensional images and an electron microscope image of the silk structure obtained by exposing an area of silk. (j) Atomic force microscopy profile of the mirco/nano pattern materials. Reproduced with permission from Ref. [124], © Springer Nature Limited 2014. (k)–(m) Different micro-nano pattern materials obtained by colloidal crystal etching technology. Reproduced with permission from Ref. [125], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2010.

with different sizes on the surface simulating non-adhesive extracellular matrix by nano-imprinting technology [106]. The micropatterns could dynamically control the deformation and polarization of osteoblasts, which provides evidence for enhancing the adhesion behavior of osteoblasts *in vitro*. In addition, by mimicking patterned substrates of different topologies of extracellular matrix, cell migration behavior can be precisely controlled in space and time, and cell migration speed can be controlled by adjusting surface ligand density [107]. Compared to micro-contact printing technology, nano-imprint lithography technology does not depend on the use of photons or electrons to change the physical or chemical properties of photolithography resins, thus avoiding a decrease in accuracy from polymer distortion and providing resolutions < 10 nm for large-scale nano-pattern preparation [108]. Therefore, the preparation of micro-nano pattern materials by nano-imprint lithography produces higher yields, higher accuracy, and lower consumption. However, high precision molds are challenging to produce because high precision molds are closely related to nano-imprinting precision, and hard molds are easy to break in the demolding process, thus creating major obstacles and challenges.

3.3 Electron beam lithography (EBL)

EBL is a micro-nano fabrication technology that uses a specific high polymer that is sensitive to electrons to form an exposure pattern (Figs. 3(c) and 3(d)). EBL is currently the highest

resolution and most flexible tool for micro-nano pattern fabrication capable of producing nano-patterns < 100 nm in size (Figs. 3(e) and 3(f)). In 1958, American scientists first utilized high energy electron beams to fabricate high resolution two-dimensional graphic structures using an etched mask, which was indeed a major breakthrough [109]. Electron-beam exposure systems mainly include three basic parts: an electron gun, an electron lens, and an electron deflector. Typically, high energy electron beams are used to act on an anti-corrosive agent of the material to create an exposure pattern on a substrate coated with photoresist, thus allowing the surface of the material to have anti-corrosive agents with different solubility in different regions. Specific areas to dissolve or preserve can be selected based on the strength of anti-corrosive agent solubility, thus obtaining micro-nano pattern structures (Fig. 3(b)) [110]. The anti-corrosive materials used for exposure mostly include polymethyl methacrylate (PMMA) and hydrogen silsesquioxane (HSQ). Chang used electron beam exposure directly to construct nano-pattern surfaces on cylindrical molds [111], while Ogih used electron beam exposure technology to manufacture gold nano-plates with a thickness of 30 nm on a quartz substrate as biosensors to fix receptor proteins [112], thus opening up new horizons for biomedical applications. Currently, electron beam exposure technology has produced fine patterns < 5 nm in size, which overcomes the resolution limitation brought by light diffraction in traditional lithography, thus arrays with nano-features can be easily obtained. The equipment complexity, low yield, and high cost are obstacles for large-scale application in the preparation of micro-nano pattern materials.

3.4 Colloidal crystal etching technology

In the construction of micro-nano pattern materials, colloidal crystal etching technology uses a self-assembling 2D or 3D colloidal crystal, such as silica microspheres, at the interface as a mask, and combines etching, deposition, and other methods to construct various ordered pattern structures through methods including magnetron sputtering, metal evaporation deposition, or plasma etching (Figs. 3(k)–3(m)). The smallest controllable size can be reduced to 20 nm [113]. In the 1980s, American scientists first used 2D colloidal crystals as masks to deposit platinum on the substrate, thus pioneering the construction of micro-nano pattern materials by colloidal etching technology [114]. Li et al. used plasma etching and other methods to prepare silicon nano-array substrates with excellent optical properties [115]. Dae-Geun and Hyung made use of changes in the surface etching angle to construct triangle-shaped micro- and nano-matrix substrates with adjustable depth and width based on 2D colloidal crystal masks [116]. Compared with traditional micro- and nano- pattern construction technology, the colloidal crystal etching technology has the advantages of low cost, simple operation, and good controllability, which is a comprehensive, high yield, and low energy consumption construction technology. Colloidal crystal-assisted controllable deposition, colloidal crystal-assisted printing, and other technologies have gradually developed [117–120]. The colloidal crystal etching technology is mainly applied to biosensors and biochips in the biomedical field, except for some applications in biological substrates [121, 122].

3.5 Self-assembly technology of block copolymers

Similar to colloidal crystal etching technology, block copolymers are a general term for high molecular weight polymers composed of two or more chains with different chemical structures connected by covalent bonds (Fig. 4(a)) [126–128]. The size of materials constructed using block copolymer self-assembly technology is influenced by the chain lengths of the two block copolymers and the preparation conditions (Fig. 4(b)), with a resolution typically ranging from 10 to 100 nm [129, 130]. Self-assembly technology of block copolymers provided a simple and effective method for preparing morphologically controllable supramolecular assemblies, which are often used to prepare highly ordered microporous structure patterns by regulating polymer composition, polymer concentration and solvent properties to mimicking the special topological morphology of extracellular matrix (Fig. 4(c)) [131, 132]. These structures could not only effectively regulate the differentiation of human mesenchymal stem cells(hMSCs) into osteoblasts, but also make neural stem cells exhibiting highly aligned and slender patterns to accelerate the degree of differentiation into neurons. Generally, three factors mainly affect the self-assembly behavior of the block copolymer to copolymer to fabricate micro-nano materials [133]: the degree of polymerization (N) of the block copolymer, the volume fraction (f_x) of each chain segment, and the Flory-Huggins interaction parameter (χ) between each chain segment. Taking block copolymers consisting of two segments as an example, the size and periodicity can be described using the following equation (Eq. (1)) [134].

$$\frac{\Delta G_{mix}}{TK_b} = \frac{1}{N_A} In(f_A) + \frac{1}{N_B} In(f_B) + f_A f_B \chi_{AB} \quad (1)$$

ΔG_{mix} is the mixing free energy, K_b is the Boltzmann constant, also known as the reaction rate constant, N_A and f_A represent the polymerization degree and volume fraction of segment A in the copolymer, respectively. N_B and f_B represent the polymerization degree and volume fraction of segment B in the copolymer, respectively. χ_{AB} is the Flory-Huggins interaction parameter between the chain segments A and B, in which the left side represents the entropy change of the system and $f_A f_B \chi_{AB}$ represents the enthalpy change of the mixed system. The morphology of the constructed micro-nano patterns is mainly determined by χ and the volume fractions of each segment. By using block copolymer self-assembly technology, orderly array structures can be constructed on the surface of materials as mask templates for micro-nano pattern materials [135, 136]. Therefore, it is possible to construct complex three-dimensional micro-nano pattern materials that cannot be obtained by traditional microfabrication technologies by changing the number of segments in the block copolymer. However, the preparation of the large-area micro-nano pattern material by the block copolymer self-assembly technology is a main challenge.

3.6 Electrospinning technology

Electrospinning technology is a simple and effective method for preparing ultrafine nanofibers, which utilizes a charged high molecular polymer solution to generate flow deformation under the action of a high voltage electric field, and finally spins the polymer solution into micro/nanoscale ultrafine fibers on the negatively charged collector through physical processes, such as evaporation and cooling (Fig. 5(a)). The diameter of the nanofiber produced by this technology is in the range of 3 nm–5 μm [138, 139]. Micro-nano polymer fibers prepared by electrospinning technology have been widely used in biomedical fields such as tissue engineering, wound healing, and cell culture due to their good biocompatibility and similarity in tissue structure. Classical tissue engineering is to combine tissues and cells in life science with engineering processing of different materials to obtain copolymer fibers and composite fibers with controllable physical and chemical properties, such as mechanical strength, surface hydrophilicity and hydrophobicity, degradation rate to improve or replace the original biological tissue. The common tissue engineering scaffolds are composed of different polymer materials

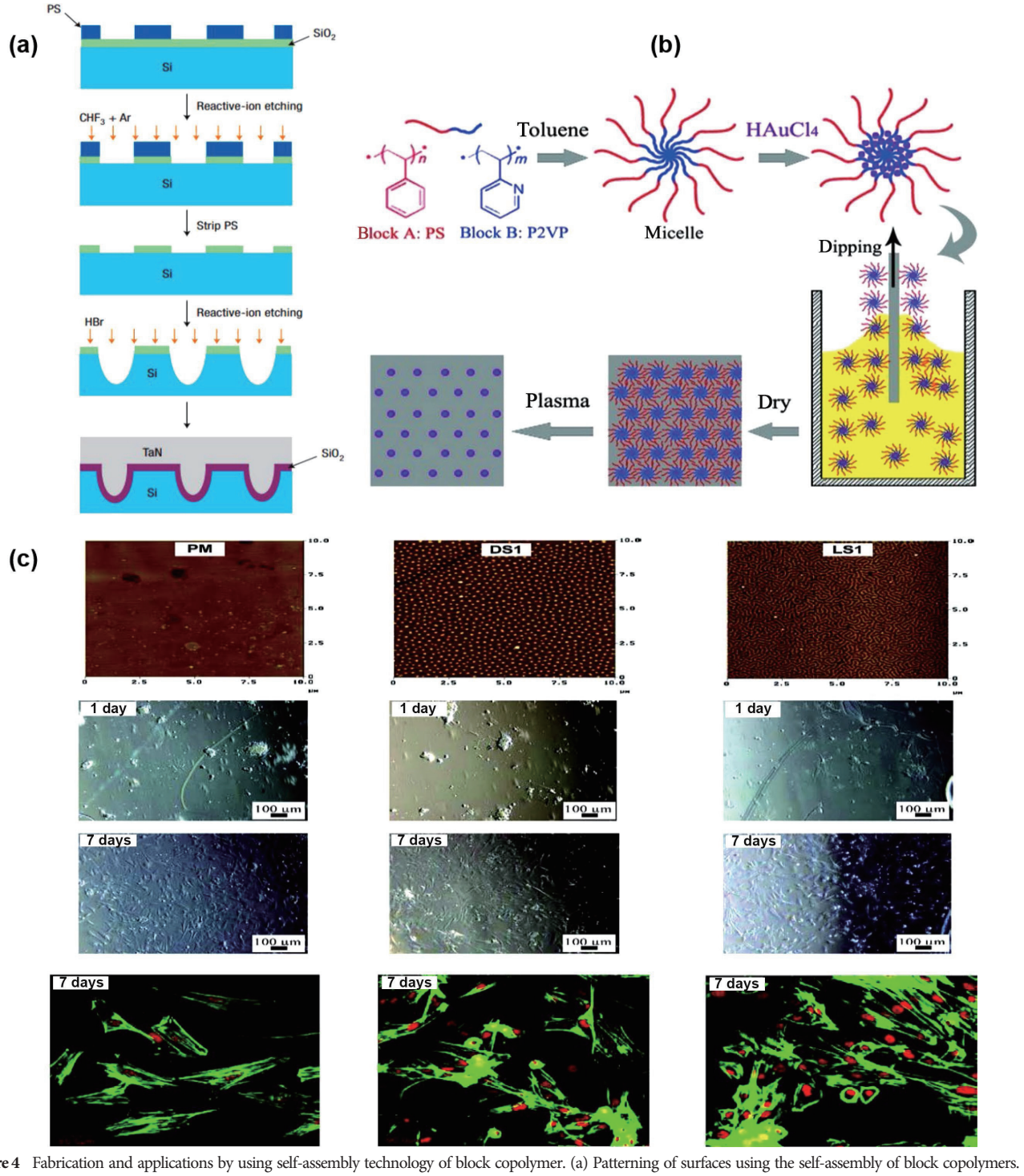

Figure 4 Fabrication and applications by using self-assembly technology of block copolymer. (a) Patterning of surfaces using the self-assembly of block copolymers. Reproduced with permission from Ref. [90], © Springer Nature Limited 1969. (b) Schematic diagram of the principle of preparing gold nanohexagonal lattice by self-assembly technology of block copolymer. Reproduced with permission from Ref. [91], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2013. (c) Cell adhesion and fluorescence images on the materials with different self-assembled morphologies. Reproduced with permission from Ref. [137], © American Chemical Society 2007.

[140–142], such as collagen, gelatin, and fibrin. Electrospinning technology, as the most effective method for continuous preparation of micro-nano fibers in large quantities, could encapsulate substances and biological macromolecules with different activities into the formed micro-nano fibers, prepare tissue models to achieve the effect of mimicking the morphology and function of diseased tissues. For example, the composite biological scaffold of polylactic acid and silk fibroin can meet the application requirements in cartilage repairment [143]. The combination of nano-hydroxyapatite and polymer can be used to prepare tissue engineering scaffolds with biological activity and excellent mechanical properties [144]. And the fiber scaffold can be prepared by electrostatic spinning of cotton cellulose/nano-hydroxyapatite (HAP) for bone tissue engineering repair, which have good thermal stability and biocompatibility to stimulate the differentiation of bone marrow stem cells into bone cells, and ultimately promoting bone repair [145]. In addition, electrospinning technology is often applied to wound repair by preparing micro/nano polymer fiber dressings to promote healing and protect wounds from further injury. Electrospun membranes made from raw materials such as polylactic acid (PLA), gelatin/PLA, chitosan/PLA, polyurethane (PU) have excellent

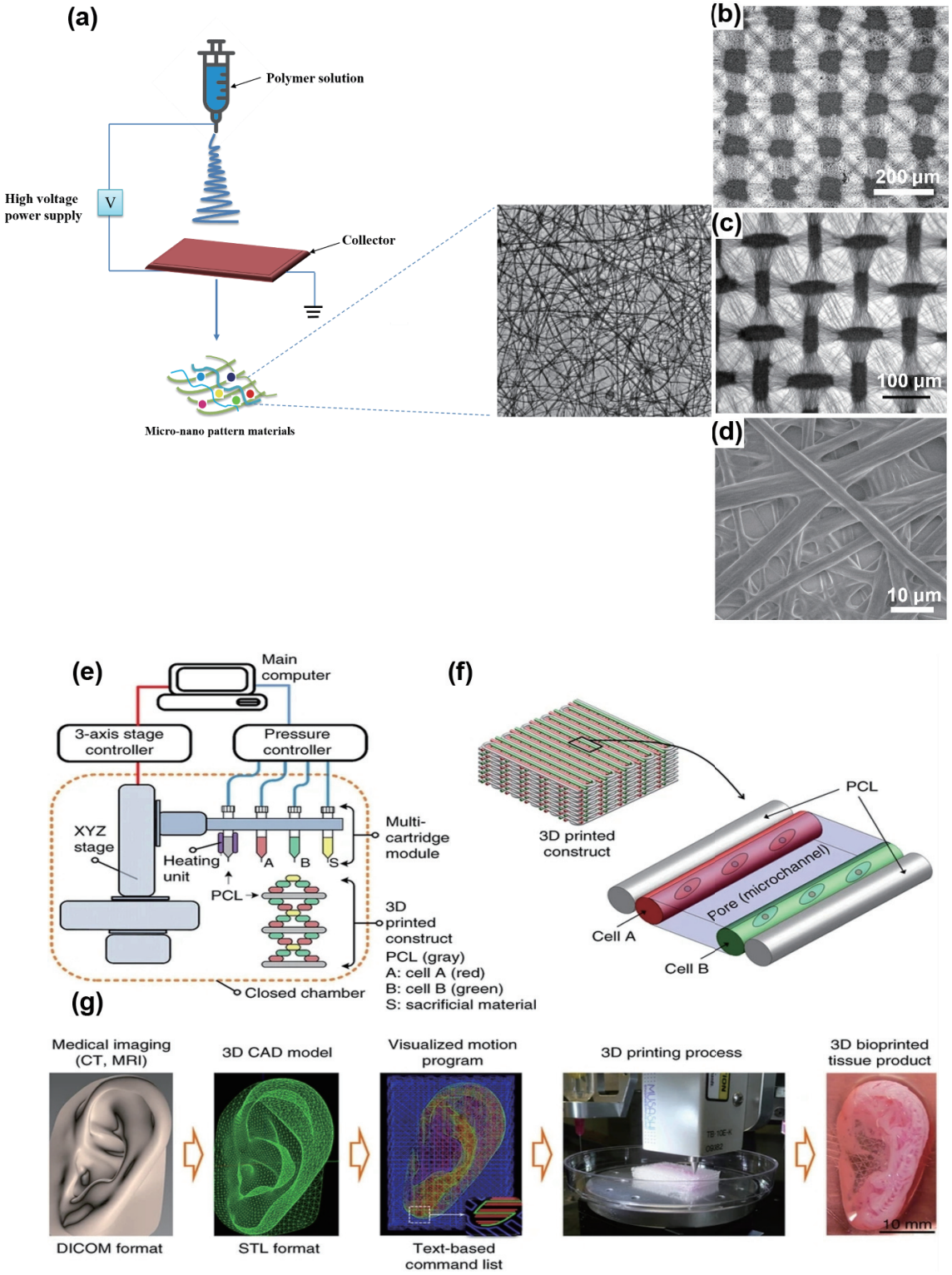

Figure 5 The electrospinning technique and three-dimensional (3D) printing technology. (a) Schematic illustration of the basic setup for electrospinning technology. Imitating the topological structure of extracellular matrix with fibers woven in a patterned arrangement of a (b) 3D nanoweb, (c) aligned and (d) crossed array. Reproduced with permission from Ref. [167], © WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 2007. Reproduced with permission from Ref. [139], © the Partner Organisations 2021. (e) Schematic diagram of the integrated 3D tissue or organ printer system including 3-axis stage/controller, dispensing module and a closed acrylic chamber. (f) Illustration of basic patterning of 3D architecture including multiple cell-laden hydrogels and supporting polycaprolactone (PCL) polymer. (g) CAD/CAM process for automated printing of 3D shape imitating target tissue or organ. Reproduced with permission from Ref. [158], © Springer Nature America, Inc. 2016.

oxygen permeability and fluid drainage ability [146, 147]. Due to their extremely small pores, these materials can still inhibit the invasion of exogenous microorganisms, thereby promoting epithelial cell differentiation and granulation tissue formation, and enabling wound recovery rapidly. Most importantly, electrospinning technology mimics the extracellular matrix for cell culture to produce polymer fibers with interconnected microporous structures and microstructures, providing a growth environment for cell growth, matrix multiplication and three-dimensional tissue generation (Fig. 5(d)). Micro-nano pattern materials with micro multi-level structures on the surface have a larger specific surface area, high porosity, three-dimensional

Table 1 Summary of patterning fabrication techniques for biomedical applications

Techniques	Scale	Limitations	Advantages	Applications	Ref.
Photolithography	Several micrometers to 100 nm	Premade mask and diffraction-limited	Stable and mass-producible	Parallel generation of arbitrary ECM patterns	[83, 84–86]
Micro-contact printing	Several micrometers	Low throughput and time-consuming	Larger areas and low cost	Soft surfaces and survival environment of cells	[96–98]
Nano-imprint lithography	Tens of nanometers	Prepatterned precision template	Simple and high throughput	Control cell deformation, adhesion and polarization	[103–107]
EBL	Several nanometers	High cost and limited materials	High accuracy and high quality	Nano-pattern structures	[110–112]
Colloidal crystal etching	Several micrometers to 20 nm	Require with other fabrication techniques	Create various ordered patterns and structures	Biological patterns and substrates	[114–116]
Block copolymers	Several nanometers	Not easy to control and require suitable molecules	Simple, effective and higher order patterns	Mimicking topological morphology, cell spreading and stem cell differentiation	[131–133]
Electrospinning	Tens of nanometers	Low accuracy and low resolution	Create fibrous meshes of biopolymers	Tissue engineering, wound healing and cell culture	[140–152]
3D printing	Tens of micrometers	Printing accuracy, consistency, and repeatability	Print animals tissue and structures	Tissue engineering and regenerative medicine	[159–163]

network structures, superior biocompatibility, and are similar in size to the structures of biological organisms. Thus, micro-nano pattern materials facilitate cell support, adhesion, and growth and are often used as tissue engineering scaffolds to simulate the ECM. Chang et al. used patterned templates as electrospinning collection templates to first prepare electrospun fiber membranes with controllable micro-patterned structures [148], which enabled preparation of patterned materials using electrospinning technology. The nanofiber materials prepared by electrospinning technology imitated the morphological structure similar to natural ECM. Schneider et al. prepared cotton-shaped patterned fiber structures of polylactic acid and tricalcium phosphate, to be used for cell culture and nerve regeneration [149]. Based on the morphological structure similar to natural ECM, it can not only play the role of supporting cells, but also play the function of extracellular matrix topology structure, providing a place for cells to grow, proliferate and differentiate. Vargas et al. used a methanol and dimethylformamide solution of polyglycerol (HPGL) to obtain biologically-active HPGL nanofiber membranes that simulate the ECM for skin damage repair [150]. As a tissue repair material, it simulates the interaction between extracellular matrix and cells, thus guiding the regeneration of damaged tissues and controlling the structure of regenerated tissues. Electrospinning-based micro-nano pattern materials can change the disordered and chaotic stacking of fibers. As a temporary substitute for biological tissues, the fiber porosity and diameter can be designed according to the shape and structure of the tissue, thus guiding cells to enter the material for growth and providing a three-dimensional living environment for cells (Figs. 5(b) and 5(c)). These scaffold structures of micro-patterns can guide cell adhesion, migration, differentiation, and matrix biosynthesis, thus meeting the requirements of tissue repair and accelerating wound healing [151, 152]. Micro-nano pattern materials fabricated by electrospinning technology have 3D network-like structures that are more suitable for the growth and adhesion of cells, have a simple preparation method and low cost, thus having great application prospects in the field of biomedical materials and regenerative medicine.

3.7 3D printing technology

In recent years, 3D printing technology has become an emerging rapid micro-nano pattern forming technology based on computer-aided design (CAD) models or data models, such as computer tomography (CT), which is also called additive manufacturing (AM) technology [153, 154]. The principle is to use laser direct writing or projection to trigger the polymerization reaction on the photo-curable material through light initiation and the photo-initiator molecules are excited to generate free radicals or cations after absorbing multiple photons. Therefore, micro-nano 2D patterns are constructed and after layer-by-layer stacking along the vertical direction, 3D micro-nano pattern materials are formed (Fig. 5(e)) [155, 156]. The application of micro-nano pattern materials constructed by 3D printing technology is increasingly broad in the biomedical field. Japanese scientists have constructed ideal vascular network models using different proportions of mixed sugars by 3D printing technology [157]. Kang et al. printed human ears by constructing models, which is difficult to achieve with traditional micro-nano pattern technology (Fig. 5(g)) [158]. In addition, Huang et al. used 3D printing molding to produce biodegradable micro-scaffolds that mimic the *in vivo* microenvironment for skin injury repair with satisfactory results [159]. These studies have broadened the application prospects of 3D printing technology in tissue engineering and regenerative medicine. Currently, there are four main technologies used to construct patterns in the biomedical field: direct ink writing technology, fused deposition modeling technology, selective laser sintering technology and stereo lithography appearance technology, among which direct ink writing technology and fused deposition modeling technology are two commonly used methods for preparing tissue engineering scaffolds. Direct ink writing technology is the most widely used bioprinting method and its biggest advantage lies in the wide range of biocompatible materials [160, 161], such as decellularized matrix dECM, cell clusters, and cell-loaded hydrogels (Fig. 5(f)). Fused deposition modeling technology is less polluting and highly recyclable [162], and is mostly suitable for manufacturing small and medium-sized biomaterial patterns with simple structures. These two methods have some problems such as long printing time, poor accuracy, and inability to print complex structures. Selective laser sintering technology not only print polymers and biocomposites, but also endow them with unique and complex structures, which has the ability to print complex tissues and supporting materials of organisms, such as orthopedics or oral surgery [163]. But its disadvantages are slow molding and high cost. Nowadays stereo lithography appearance technology, also known as micro-nano 3D printing technology [164], has higher printing resolution, accuracy and repeatability, and has unparalleled advantages in constructing complex micro-nano patterns, which is expected to replace direct ink writing technology as the most mainstream biological 3D printing technology in the future. According to the Abbe

diffraction limit, the resolution of micro-nano 3D printing mainly depends on the diffraction limit of the optical system [165], which is calculated as $0.61\lambda/NA$, where λ and NA represent the wavelength of the light source and the numerical aperture of the imaging system, respectively. Therefore, both single and two photon aggregation micro-nano 3D printing technologies still face many problems in preparing pattern materials with linewidths < 100 nm, such as difficulties in ensuring printing accuracy, consistency, and repeatability. Currently, the latest micro-nano-scale 3D printing technology can achieve efficiency, low cost, and large-scale manufacturing in constructing micro-nano pattern materials by super-resolution microscopy imaging technology and improving the resolution to < 10 nm [166].

4 Conclusion and perspectives

The topological pattern structure of materials is crucial to the occurrence of cellular behavior, and the size on the micro- or nano-scale directly determines whether cell-specific biological behavior occurs. By using technologies, such as photolithography technology, electron-beam lithography, and 3D printing technology, they can be used to fabricate suitable micro-nano pattern materials to simulate the topological structure of the ECM. The ultimate goal is to establish a natural biomechanical interface that simulates the topological pattern of the ECM by accurately controlling the surface pattern structures to study the substrate-cell interaction and cell biology problems.

In addition to the building conditions and fabrication technologies, the fabrication of suitable micro-nano pattern materials also needs to consider the chemical properties of the materials. First, micro-nano pattern materials need to meet the requirements of non-toxicity [168, 169] and good biological compatibility [170, 171]. Second, the prepared micro-nano pattern materials need excellent surface activity for biochemical modification [172–174]. Furthermore, the excellent chemical composition of the materials, appropriate hydrophilic [175] and hydrophobic properties with a specific charge [176, 177], and the roughness and curvature of micro-nano pattern materials also have an important role in simulating the ECM [178, 179]. With the maturity and development of various pattern fabrication techniques, many micro-nanoscale and large-area patterns need to be cleverly combined with different techniques. Moreover, the complexity of morphology (2D and 3D) and the chemical composition of materials need to be increased to better mimic biological tissues and organs. The fabrication of micro-nano patterned materials will have significant application value in tissue engineering, biomaterials, and regenerative medicine in the future.

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