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Interfacial nanoarchitectonics for responsive cellular biosystems

Jingwen Song [a], Xiaofang Jia [b], Katsuhiko Ariga [a,b,*]

[a] Department of Advanced Materials Science, Graduate School of Frontier Sciences, The University of Tokyo, 5-1-5 Kashiwanoha, Kashiwa, Chiba, 277-8561, Japan
[b] World Premier International (WPI) Research Center for Materials Nanoarchitectonics (MANA), National Institute for Materials Science (NIMS), 1-1 Namiki, Tsukuba, 305-0044, Japan

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ABSTRACT

The living cell can be regarded as an ideal functional material system in which many functional systems are working together with high efficiency and specificity mostly under mild ambient conditions. Fabrication of living cell–like functional materials is regarded as one of the final goals of the nanoarchitectonics approach. In this short review article, material-based approaches for regulation of living cell behaviors by external stimuli are discussed. Nanoarchitectonics strategies on cell regulation by various external inputs are first exemplified. Recent approaches on cell regulation with interfacial nanoarchitectonics are also discussed in two extreme cases using a very hard interface with nanoarchitected carbon arrays and a fluidic interface of the liquid-liquid interface. Importance of interfacial nanoarchitectonics in controlling living cells by mechanical and supramolecular stimuli from the interfaces is demonstrated.

1. Introduction

From the nanoscale to macroscopic scale, conversions of materials, signals, and information are keys for functions in many cases, including regulation of material functions by external stimuli [1–3], energy production from external energy sources [4–6], energy management on external input [7–10], various information conversions from inputs to outputs [11–13], and controls of biological responses [14–17]. The design and fabrication of functional materials and systems for these conversions with high efficiency and desired specificity are crucial matters for various social demands such as energy [18–20], environmental [21–24], and biomedical [25–27] issues. The synthetic efforts by organic chemistry [28–30], polymer chemistry [31–33], supramolecular chemistry [34–36], and materials sciences [37–41] used to be limited tools to create desired functional materials. However, rapid developments of biotechnology [42–44] and nanotechnology [45,46] open novel ways to understand and control precise nanolevel phenomena.

Biotechnology reveals sophisticated molecular functions in many biological systems. The living cell can be regarded as an ideal functional material system for conversions of materials, signals, and information. Many functional systems are working together with high efficiency and specificity under mild ambient conditions. In most cases, precisely designed molecular mechanisms lead to these sophisticated functions [47,48]. The precise architecture strategy seen in living cells would be applicable to design and synthesis of non-biofunctional material systems. For the latter targets, advanced observation and manipulation of nanolevel structures in nanotechnology probably have indispensable contributions [49–51]. Material fabrications with advanced knowledge of nanoscience and nanotechnology would be effective approaches to produce highly functional living cell–like material systems. Therefore, fusion of nanotechnology with the other research disciplines such as organic chemistry, supramolecular chemistry, materials science, and biology is necessary for the revolution of material fabrication.

This task is taken by an emerging concept, nanoarchitectonics [52]. Similar to the nanotechnology concept originated by Richard Feynman [53,54], the nanoarchitectonics concept was originated by Aono [55], Ariga et al [56], and Ariga and Aono [57]. There are plenty of unexplored sciences in nanoscale bottoms as proposed by nanotechnology, but huge possibilities to produce functional materials actually remain in nanoarchitectonics processes from bottom-scale objects to materials. While nanotechnology mainly focuses on analyses and manipulation of nanoscale systems, nanoarchitectonics is charged for construction of functional materials from nanoscale objects. The nanoarchitectonics approach aims to fabricate functional materials with nanoscale units for final goals to create living creature–like functional systems [58,59]. Functional material systems are architected from nanoscale units through combined actions and/or selected efforts of nanotechnology-based manipulation, organic synthesis, self-assembly/self-organization,

* Corresponding author.
E-mail address: ARIGA.Katsuhiko@nims.go.jp (K. Ariga).

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field-induced assembly, nanofabrication and microfabrication, and bio-related processes [60,61] (Fig. 1). Because this synthetic strategy can be applicable to a wide range of functional materials, the nanoarchitectonics concept is proposed to be applied to various fields including material production [62–64], structure fabrication [65,66], energy [67,68], catalysis [69,70], sensors [71–73], devices [74,75], and environmental targets [76,77]. Especially, the nanoarchitectonics approaches coupling with biological basic studies [78–80] and biomedical applications [81,82] have been paid rather intense attentions.

The construction of functional systems by the nanoarchitectonics approach shares common features with biological systems such as living cells, especially from the following two viewpoints. One of them is the high potential in production of hierarchical structures [83]. Although the nanoarchitectonics concept uses processes similar to self-assembly, non-equilibrium and multistep constructions are often included into the nanoarchitectonics approach unlike the conventional self-assembly process. This feature of nanoarchitectonics is advantageous for the fabrication of hierarchical material systems, which is rather close to complicated self-organization for hierarchical biosystems. Another distinct feature of the nanoarchitectonics approach is the necessity of coupling of various interactions with uncertainties in nanoscale phenomena [84]. In the nanoscale regions, various uncertainties such as thermal fluctuation, static distributions, and quantum effect as well as complex mutual interaction among individual components cannot be avoided. Therefore, the combination of many effects and interactions often becomes important in the nanoarchitectonics approach rather than simple summation of individual effects. This situation is similar to those commonly observed in biological systems in which various functional molecular systems are working with unavoidable thermal fluctuations.

These features make the nanoarchitectonics concept a powerful approach to fabricate biolike sophisticated functional systems such as living cells. Although fabrication of living creature–like functional materials is regarded as one of the final goals of the nanoarchitectonics approach, the construction of even a single cell–equivalent functional system is currently a tough target. Instead of constructing the whole cell–like structures, the conjugation of artificial nanosystems and actual living cells would be an accomplishable target to control cell behaviors. From this viewpoint, the material-based approaches for the regulation of living cell behaviors by external stimuli are discussed especially in this short review article. For this focused target, nanoarchitectonics material approaches on cell regulations by various external inputs such as electronic, photonic, mechanical, thermal, and magnetic stimuli are exemplified in the following sections. These examples indicate indispensable contributions of interactions at interfaces between cells and materials despite a huge variety of stimuli inputs. Fundamental consideration on interfacial features of cell behaviors is undoubtedly important. Therefore, in later sections, recent approaches on cell regulation with interfacial nanoarchitectonics are discussed in two extreme cases using a very hard interface with nanoarchitected carbon arrays and a completely fluidic interface of the liquid-liquid interface. The importance of interfacial nanoarchitectonics on controlling living cells from mechanical and supramolecular stimuli from the interfaces is demonstrated. In selected examples, nanoarchitectonics, structural fabrications, and organization using nano and molecular units are keys for specific responding behaviors of contacting cells.

2. Electronic stimuli

Inputs of electronic stimuli are commonly seen in artificial device systems and stimulus-responsive materials [85–88]. Similarly, electronic stimuli are also used in regulation of living cells. Advanced bioelectronic materials provide new tools to control cell functions by electrical communication between the interface of the cell and substrate. It is a challenge to generate bioelectronic materials with the properties of low impedance, sufficient biofunction, and stimulus responsiveness for achieving the requirements of efficiently electrical communication, biocompatibility, and controlling cell behavior [89]. Lin et al. [90] constructed a dynamic poly(3,4-ethylenedioxythiophene) (PEDOT) film based on a hydroquinone-functionalized 3,4-ethylenedioxythiophene (EDOT) and zwitterionic phosphorylcholine–functionalized EDOT. The dynamic PEDOT film provides a clear electroresponsive oxime switch for addressing surface functions spatiotemporally based on the benzoquinone-hydroquinone electroredox interconversion (Fig. 2). The phosphorylcholine-grafted dynamic PEDOT material provides strong resistance to the non-specific interaction in physiological environments, ensuring stable and efficient electrical communication with cells. More

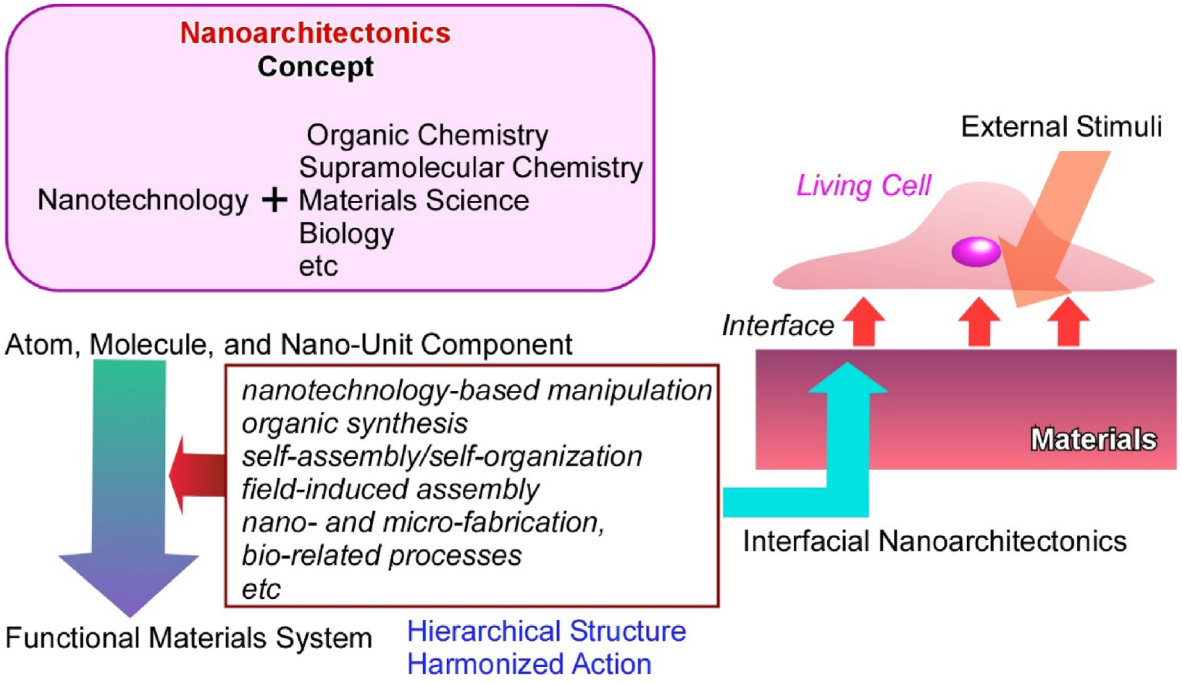

Fig. 1. Outline and features of the nanoarchitectonics concept for the regulation of the living cell.

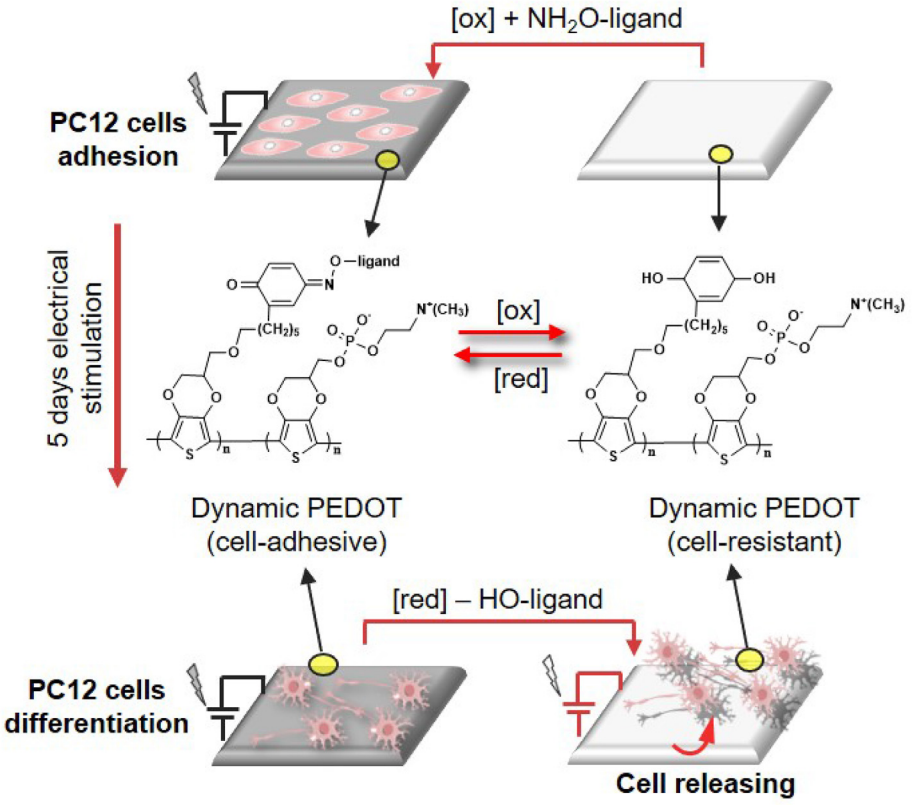

Fig. 2. The dynamic poly(3,4-ethylenedioxythiophene) (PEDOT) films spatiotemporally control cell attachment, detachment, and differentiation by a clear electroresponsive oxime switch: [red]; reduction, [ox]; oxidation [90].

significantly, the dynamic PEDOT film provides an ideal electronic interface for neural differentiation after 5 days of electrical stimulation and culturing. It also can spatiotemporally control cell attachment and detachment by redox-responsive characteristics.

Direct conversion provides an appealing strategy to generate effective cell therapeutics for neuronal degeneration without using limited stem or progenitor cells. Non-viral direct conversion accelerated by electrical stimulation can be considered to enhance the safety issues and conversion efficiency of fibroblasts to induced neuronal cells. The triboelectric nanogenerator is an up-and-coming mechanical energy-harvesting device, as one of the most prospective candidates for developing implantable electronics. It can generate electricity continually from human motion in a quite simple, cost-effective manner. Jin et al [91] established a triboelectric stimulation platform to accelerate non-viral direct conversion with high safety and efficiency for obtaining induced neuronal cells (Fig. 3). Genes encoding neuronal lineage–specific transcription factors *Brn2*, *Ascl1*, and *Myt1l* were carried by biodegradable polymeric nanoparticles and delivered into fibroblasts through electroporation. The

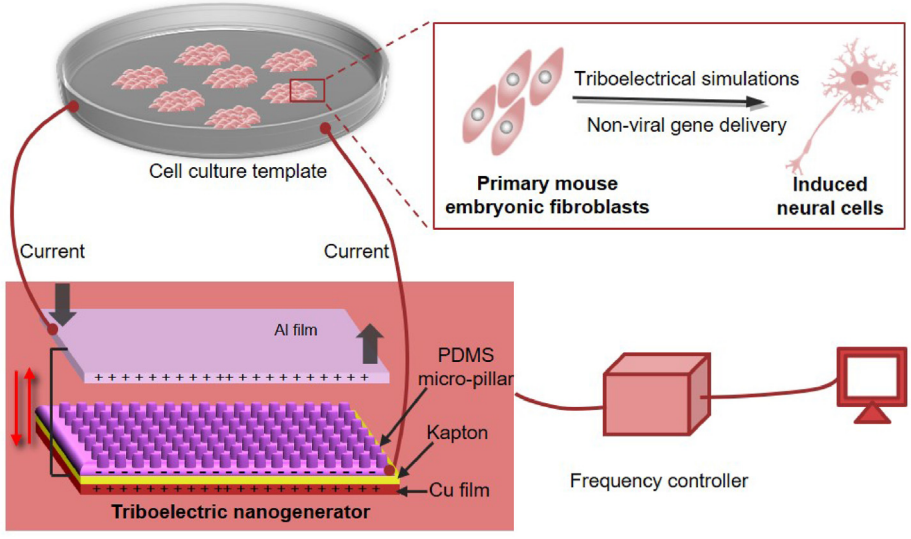

Fig. 3. A triboelectric stimulation platform accelerates non-viral direct conversion with high safety and efficiency for obtaining induced neuronal cells [91]. PDMS, polydimethylsiloxane.

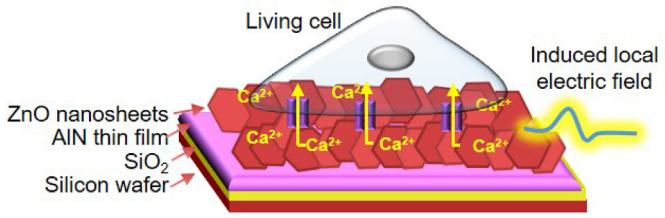

Fig. 4. The two-dimensional ZnO nanosheet–based piezoelectric nanogenerator can be used for electrical stimulation of living cells. The electromechanical nanogenerator-cell interactions activate the opening of the Ca^{2+} channels in the plasma membrane of cells [94].

stimulated fibroblasts underwent an accelerated transdifferentiation to the highly matured neuronal phenotypes of induced neural cells. Furthermore, this triboelectric nanogenerator platform greatly enhanced *in vivo* generation of induced neural cells in the mice skin tissues and improved electrophysiological functionalities.

Nanogenerators opened new frontiers in biological applications based on the non-invasive methods for in situ controllable electrical stimulation [92,93]. As we know, the intracellular tension of living cells can be transmitted to the underlying nanogenerator substrate by focal contacts. Consequently, the inherent forces generated by the cell would create an electric field around the cell plasma membrane. Nanostructured ZnO has become widely used in piezoelectric nanogenerators with the properties of voltage generation when mechanically stressed. Murillo et al [94] designed and constructed a network of ZnO nanosheets as piezoelectric nanogenerators, which can be used for electrical stimulation of living cells (Fig. 4). A local electric field on the ZnO nanosheet-cell interface was induced by piezoelectric nanogenerators for modulating living cellular activity and behavior when cells were cultured on the top of the ZnO nanosheet surface. The interactions between the electromechanical nanogenerator and cells can stimulate the motility of macrophages and induce intracellular calcium transients of osteoblast-like cells (Saos-2). Importantly, this nanogenerator exhibited excellent cell viability, proliferation, and differentiation when Saos-2 was cultured for up to 14 days. Moreover, this in situ cell-scale electrical stimulation could be extrapolated to other types of cells such as neural cells or muscle cells. The ZnO nanosheet–based nanogenerators provide an appealing strategy based on cell-targeted electrical impulses for the future bioelectronic medical treatment.

Material-based dynamic biointerfaces offer a prospective strategy to define cell functions by bioimitating extracellular matrix. However, the performance and design of artificial biointerfaces cannot be compared with *in vivo* cell niches that can temporally and exactly provide reversibly physical and chemical stimuli from macroscale to nanoscale. Wei et al [95] constructed a dynamic platform based on reversibly electrochemical switching of a polypyrrole array between highly adhesive hydrophobic nanotubes (electrochemical oxidation) and poorly adhesive hydrophilic nanotips (electrochemical reduction). The polypyrrole array substrate under electrochemical stimuli can switch the attachment and detachment

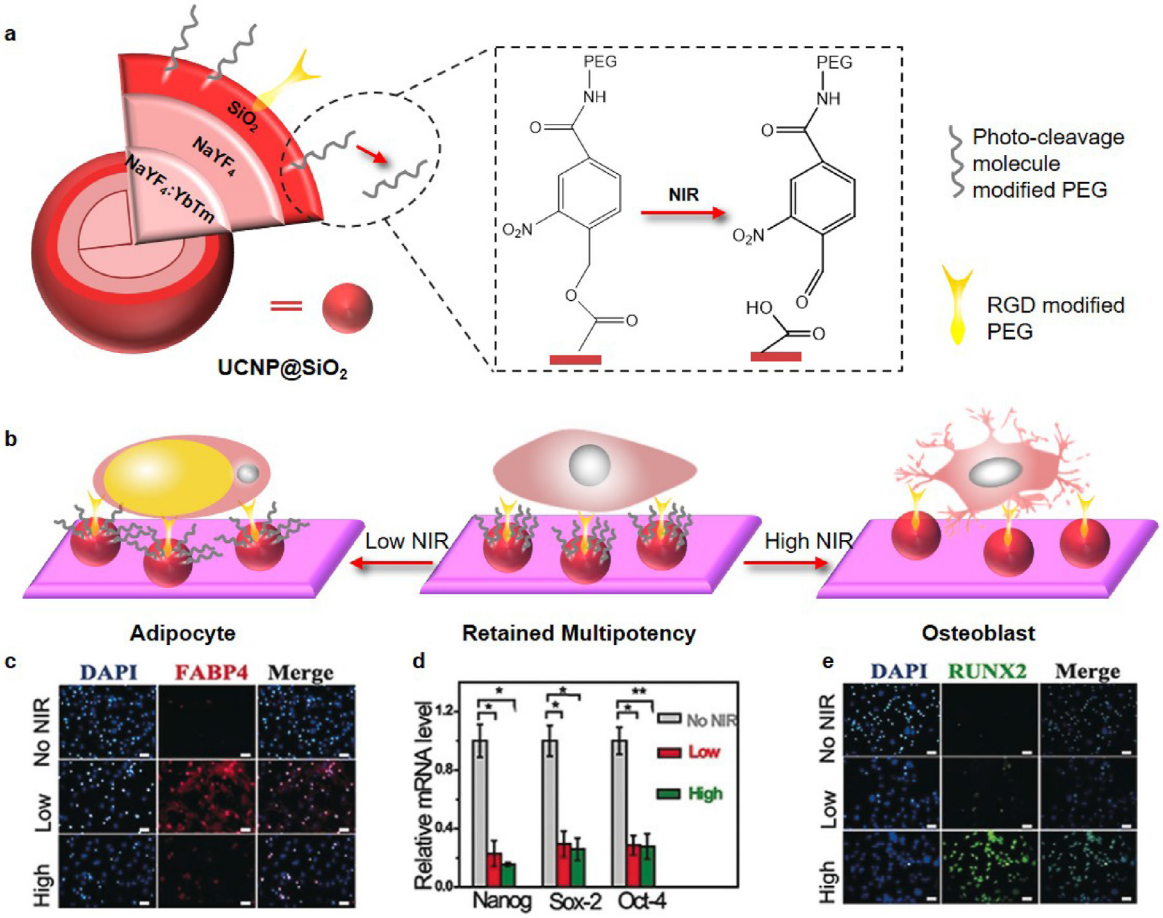

Fig. 5. (a) The photocontrolled UCNP-based cell-cultured substrates are coated with the antiadhesive effect of photocleavage molecule–modified PEG. (b) Depending on the NIR irradiation, the PEG molecules are released from the cell culture substrates to regulate cell-extracellular matrix interactions dynamically and then modulate MSC self-renewal or differentiation to adipocytes or osteoblasts. (c) Immunofluorescence imaging of adipogenic markers (FABP4, red). (d) The expression of the multipotency gene, *Nanog*, *Sox2*, and *Oct4* ($^*p < 0.05$, $n = 3$). (e) Immunofluorescence imaging of adipogenic markers (RUNX2, green). Scale bar: 50 μm; DAPI and UCNP: please see reference [102]. Copyright 2018, WILEY-VCH. NIR, near-infrared; PEG, poly(ethylene glycol); RGD, arginylglycylaspartic acid; MSC, mesenchymal stem cell.

of mesenchymal stem cells at nanoscale. Moreover, this electrochemical substrate can dynamically control the mechanotransductive activation and guide the fate of mesenchymal stem cells. Multicyclic attachment/-detachment of mesenchymal stem cells on the polypyrrole array substrate can control cytoskeleton organization, YAP/RUNX2 translocation, and osteogenic differentiation mediated by intracellular mechanotransduction without the influence of surface stiffness and chemical induction. This smart surface represents an alternative cell culture substrate for exploring nanoscaled stimulus-responsive surfaces how to influence stem cell fate commitment.

There is a great need for bioelectric materials with selective and efficient capability to provide electrical interfaces for neural regeneration and without being recognized by the immune system to minimize the immune response. PEDOT as electrically conducting polymers can provide excellent and stable electrical communications with adhered cells and tissues for neural regeneration process. To prevent the inflammatory response and scar formation, Zhu et al [96] followed a cell membrane–mimicking approach to synthesize PEDOT by polymerizing the zwitterionic phosphorylcholine–functionalized EDOT and the maleimide-functionalized EDOT. Then, they achieved conjugation of the specific peptide sequence Ile-Lys-Val-Ala-Val by ligand-receptor interactions to obtain the biomimetic PEDOT. As neural bioelectronics, the biomimetic PEDOT devices have the inherent capability to prevent non-specific binding of proteins and cells. Therefore, this biomimetic PEDOT substrate presents the capability of integrating biochemical and electrical stimulation and minimizing the immune response. PC12 cells cultured on this material largely enhanced neurite outgrowth by electrical stimulation. These designed electrically conducting polymers are critical and desired bioelectronic devices for the applications of nerve regeneration, neuroprosthetic devices, and biosensors.

3. Photonic stimuli

Photonic stimuli such as light irradiations are frequently used in a wide range of stimulus-responsive materials because they are applicable by adjusting the energy level (wavelength) by space ways without the need of contacting [97,98]. In cell regulation technology, photonic stimuli are also useful sources of stimuli inputs [99,100].

Engineering extracellular matrices is an effective way to control stem cell fate. Smart artificial interface biomaterials are typically easy to modify with functional molecules, which can dynamically control stem cell fate from self-renewal to differentiation by a simple physical or chemical microenvironmental change [101]. Lanthanide-doped upconversion nanoparticles are good candidates for on-demand manipulating cell behavior owing to their intrinsic properties of absorbing near-infrared (NIR) light and converting into high-energy of ultraviolet (UV), visible, or NIR irradiation. Yan et al [102] designed and prepared a upconversion nanoparticle-based cell-cultured substrate by molecular engineering (Fig. 5). They modified the anti-adhesive effect of poly(ethylene glycol) (PEG) on the photocontrolled upconverted lanthanide-doped upconversion nanoparticle substrate. Depending on the NIR irradiation, the PEG is released from the cell culture substrate by the photocleavage process to regulate cell-extracellular matrix interactions dynamically and then modulate mesenchymal stem cell self-renewal or differentiation to adipocytes or osteoblasts. This work provides a new strategy to regulate the multipotent differentiation of mesenchymal stem cells by using the NIR-based upconversion materials.

Strategies of controlled and non-invasive cell harvesting are required in biomedical research, regenerative therapy, and tissue engineering. The light in the NIR irradiation stands out as one of the most convenient triggers for cell detachment without irreversibly damaging cells. Giner-Casares et al [103] designed a two-dimensional gold nanoparticle array with a broad absorption spectrum range including a wide part of visible and NIR light to form a versatile platform for cell growth and retrieval. They functionalized the surface of Au nanoparticles via simple thiol chemistry for growing a variety of cell types. Biofunctionalization with the cyclic arginylglycylaspartic acid (c-RGD) peptide could regulate the morphology of integrin-rich cells. In addition, highly efficient detachment of the cell sheet with cell viability was obtained by photothermal effect by irradiation using a 980-nm NIR laser. This procedure provides a non-invasive strategy for forming cell organization. Moreover, the photothermal effect generated by Au nanoparticles was identified as the main reason of cell detachment. The nanoplasmonic surfaces for cell culture and highly efficient detachment using non-invasive NIR light provide a huge potential in regenerative medicine and tissue engineering.

Biomaterials with temporal and spatial presentation of the bioadhesive epitopes using external triggers under *in vivo* culture conditions can be exploited to elicit targeted tissue reparative response. Lee et al [104] developed light-triggered cell-adhesive materials using the c-RGD modified with a photolabile caging group, 3-(4,5-dimethoxy-2-nitrophenyl)-2-butyl ester, on the aspartic acid residue. The ligand RGD can be spatially controlled to expose *in vivo* via transdermal light irradiation. Their results demonstrate that *in vivo* light triggering the presentation of the cell-adhesive RGD peptide can promote vascularization and endothelial cell function, and delaying the presentation time of the ligand RGD can significantly reduce the chronic inflammatory responses and fibrosis to implanted biomaterials. This non-invasive, transdermal time-regulated, photoresponsive hydrogels for the temporal presentation of ligands on implanted biomaterials can regulate cell adhesion, inflammation, and vascularization of tissue-reparative responses. However, this research focused on a UV light irradiation–activated photoreaction. The UV light trigger is limited in *in vitro* applications owing to the low penetrated depth for biological tissue and targeted biomaterials.

Controlling the size (from the nanometer to micrometer scale) and arrangement of topographic features as extracellular matrix cues is known to have a great impact on cell adhesion, morphology, migration and differentiation, and tissue organization [105]. Recapitulating dynamic changes of topography in stimulus-responsive materials has become an important approach to generate the microenvironment that closely mimics the biosystem *in vivo* for cell therapy. Koçer et al [106] designed light-responsive liquid crystal polymer networks with the adaptive and programmable nature to generate a new spatial arrangement of patterned biointerfaces for dynamically guiding cell behavior. The (meth)acrylate-functionalized azobenzene mixed with liquid crystalline monomers was used for creating a chiral nematic phase that was aligned in a flat through shear forces and was then photopolymerized to a film. Mask irradiation of the film leads to in situ *trans*-to-*cis* isomerization of azobenzene molecules, resulting in an in situ formation of protrusions in the irradiated areas yielding topographical morphology. In situ temporal changing the nanoroughness and the height of micropile of the hierarchical structure surface could direct cell migration and adhesion.

The surrounding biophysical environment of cells and tissue can have a dramatic impact on biological processes involving the recruitment of cells to a specific site during wound healing or disease development. However, it is challenging to identify the subcellular, spatial mechanical stimulation on the microenvironment and to investigate how such different variations of mechanical stimulation integrate to influence local cellular activity. Yang et al [107] prepared the photoresponsive cell culture substrates by using PEG with photolabile linkages (Fig. 6). These hydrogel substrates allow for local softening of the material modulus to generate a user-tunable pattern by controlled irradiation exposure through a photomask. Human mesenchymal stem cells with high spreading and higher nucleus localization of Yes-associated protein were observed on hydrogel substrates with a higher density of regularly patterned stiff regions. However, keeping the density of stiff regions constant and altering the spatial pattern of the stiff regions from ordered to random, less active Yes-associated protein with low spreading was induced in human mesenchymal stem cells. They demonstrated that compared with ordered patterns, the irregular, disordered matrix mechanics lead to maintenance of stemness of human mesenchymal stem

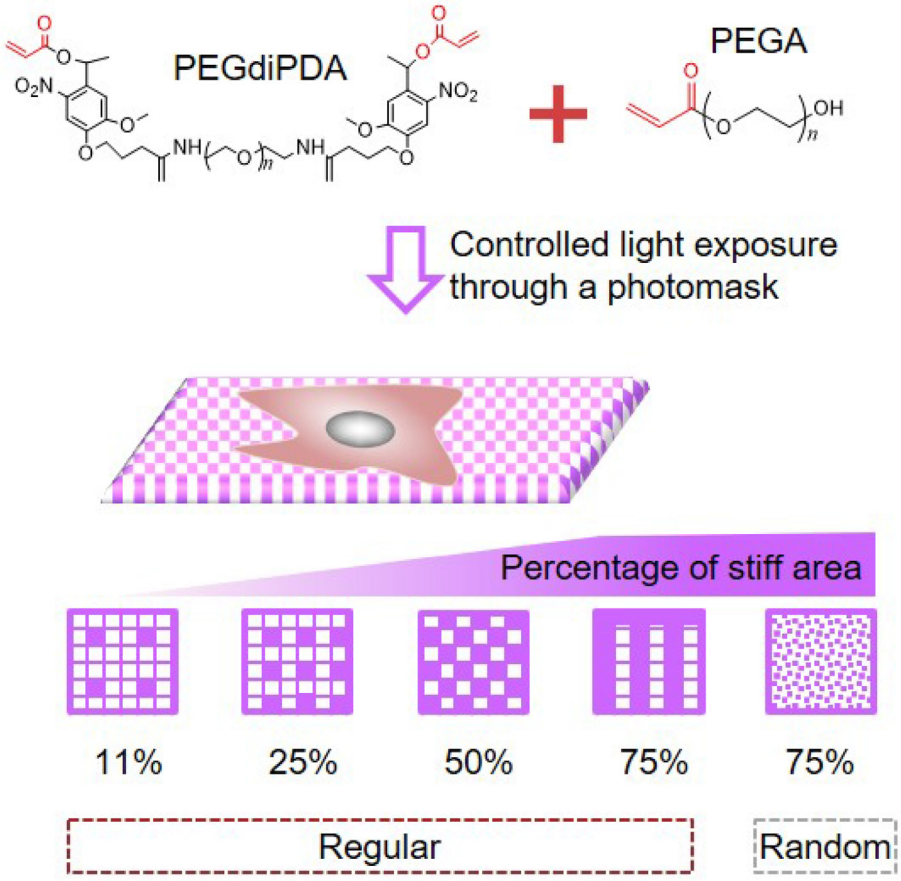

Fig. 6. Photoresponsive cell culture hydrogel substrates are prepared by copolymerizing PEG monoacrylate (PEGA) with the photodegradable cross-linker (PEG diacrylate [PEGdiPDA]) [107]. This substrate allows locally softening of the material modulus by controlling light exposure to generate a user-tunable pattern for regulating the fate of human mesenchymal stem cells. PEG, poly(ethylene glycol).

cells by disrupting the organization of actin, reducing the alkaline phosphatase activity, and inducing the higher expression of the stem cell marker CD105.

4. Mechanical stimuli

Mechanical actions are everywhere in all the length scale. Living cells have many opportunities to be exposed to external mechanical stresses. Because living cells are sensitive to mechanical forces caused by certain interactions, mechanical stimuli would be important external inputs to regulate living cells [108–111].

The physiological microenvironment in living organisms is composed of diverse biological materials with hierarchically structured assemblies and varying mechanical attributes. In addition, this microenvironment is much more complicated than conventional materials owing to the existing stiffness gradients. It remains a challenge to design a platform that represents the gradients of extracellular matrix stiffness independently of the topographic and compositional factors over a wide lateral span, which is crucial for understanding the influence of extracellular matrix stiffness gradients alone to collective cell migration. Cai et al [112] developed the mechanotactic hybrid that incorporated a microstructured SU-8 photoresist replica with high stiffness into a compliant polyacrylamide hydrogel layer. This bioinspired mechanotactic hybrid comprised the microstructured rigid layer and superficial compliant layer to resemble a physiologically effective interface for modulating cell physiology. The compliant-rigid hybrids enabled programmable lateral variation of apparent stiffness and established a mechanistic coupling of epithelial migration with extracellular matrix stiffness alone. This concept of hierarchically mechanical hybrids sheds light on the design of the next generation of bioinspired scaffolds.

To mimic the function of human's motion memory, Liu et al [113] developed a mechanical hybrid substrate that was a combination of the soft polydimethylsiloxane (PDMS)/rigid SU-8 flake–based stretchable devices with zeolitic imidazolate framework-8 (ZIF-8)–based memory device. In the hybrid film, rigid SU-8 flakes were embedded in a PDMS substrate, and then, Au films, patterned ZIF-8 thin films, and Ag films were coated on the substrates sequentially to fabricate stretchable memory devices. This hybrid substrate was spatially separated into patterned domains with different mechanical properties that can exhibit different localized strain by exerting physical forces. The rigid memory devices and stretchable strain sensors in these stretchable motion memory devices are integrated into a single module, which enables them to work cooperatively in the wearable state for health monitoring and medical applications. This work provides an instructive and valuable strategy in designing materials combined with electronic technology to achieve wearable electronic devices with integrated functions, which play a critical role in developing smart modules and future intelligent systems.

Cells *in vivo* continually interact with their microenvironment. Precise mechanical properties of cell niches from the subcellular scale up to the organ scale are important for tissue development, function, and remodeling. To mimic vital physiological conditions such as heart beating, pulsating blood vessels, and breathing, Livne et al [114] studied cell reorientation in response to cyclic stretching of the underlying substrate from both the experimental and theoretical viewpoint. From the experimental viewpoint, they observed the reorientation of focal adhesions

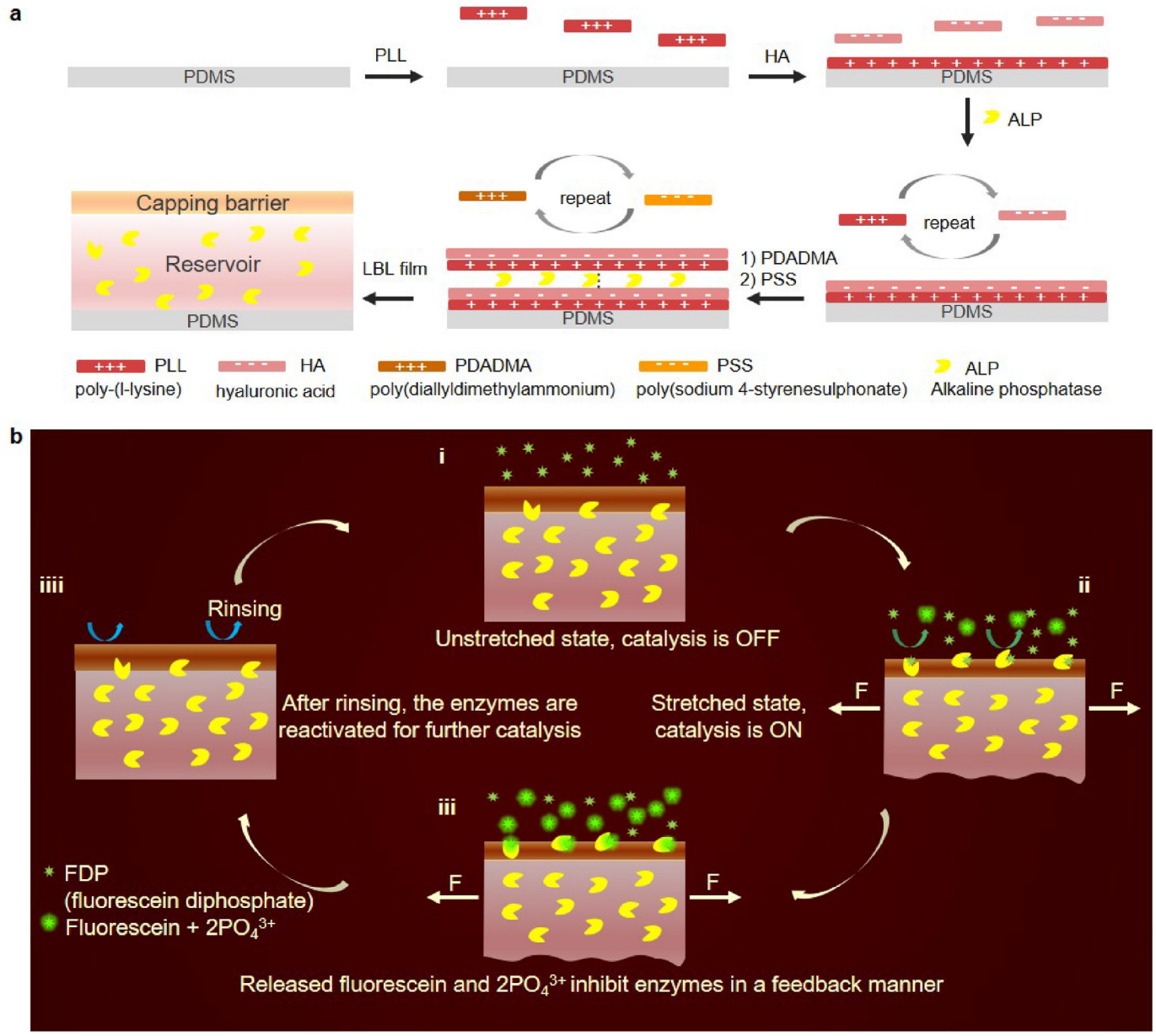

Fig. 7. (a) Biocatalytic active reservoir was deposited on the polydimethylsiloxane (PDMS) substrate by layer-by-layer technique. (b) Stretch-reversed reservoir film leads to fluorescein diphosphate (FDP) controllably hydrolyzing to strongly fluorescent fluorescein by ALP [117]. PLL, poly-(L-LYSINE); HA, HYALURONIC ACID; PDADMA, POLY(DIALLYLDIMETHYLAMMONIUM); PSS, POLY(SODIUM 4-STYRENESULPHONATE); ALP, ALKALINE PHOSPHATASE.

and the rotation of stress fibers under applying cyclic stretching. Then, they developed a new theory, which considers both the passive mechanical response of the cells to deformation of the substrate and the active remodeling response of their stress fibers and focal adhesions. This theory highlighted the interplay among the structure, elasticity, and molecular kinetics in the cell reorientation process. They showed that dissipative relaxation of the cells' passively stored, two-dimensional, elastic energy to its minimum actively drives the cell reorientation process. The theory provides a new first-principles approach that significantly enhances our comprehension of cellular mechanosensing.

Targeted delivery of nanoparticles to malignant cells and tissues provides a platform for next-generation diagnosis and therapy. To improve the efficiency of targeted delivery, the cellular uptake of nanoparticles ought to bias toward malignant cells. Compared with chemotargeting, mechanotargeting (mechanics-dependent cellular uptake of nanoagents) as a new targeting strategy drives biased uptake based on the difference of cell surface mechanics. Wei et al [115] developed *in vitro* experiments to demonstrate the working mechanism of mechanotargeting. They seeded human cervical cancer HeLa cells and human colon carcinoma cells on the surfaces of hydrogel of different stiffnesses to direct these two lines of the cell into different stress states. Targeted delivery of nanoparticle-based diagnostic and therapeutic agents to malignant cells and tissues was shown to rely on mechanotargeting. They demonstrated that increase in cell stress prefers to suppress cellular uptake, counteracting the enhanced cellular uptake that occurs with increases in the exposed surface area of spread cells. Hence, to activate mechanotargeting bias toward malignant cells in the stiff high-stressed tumor microenvironment, one may first add myosin contraction inhibitor or alter the local environment of the cells to reduce the stress state. In addition, one may optimize the size and stiffness of nanoparticles to modulate the deformation energy of the cell membrane.

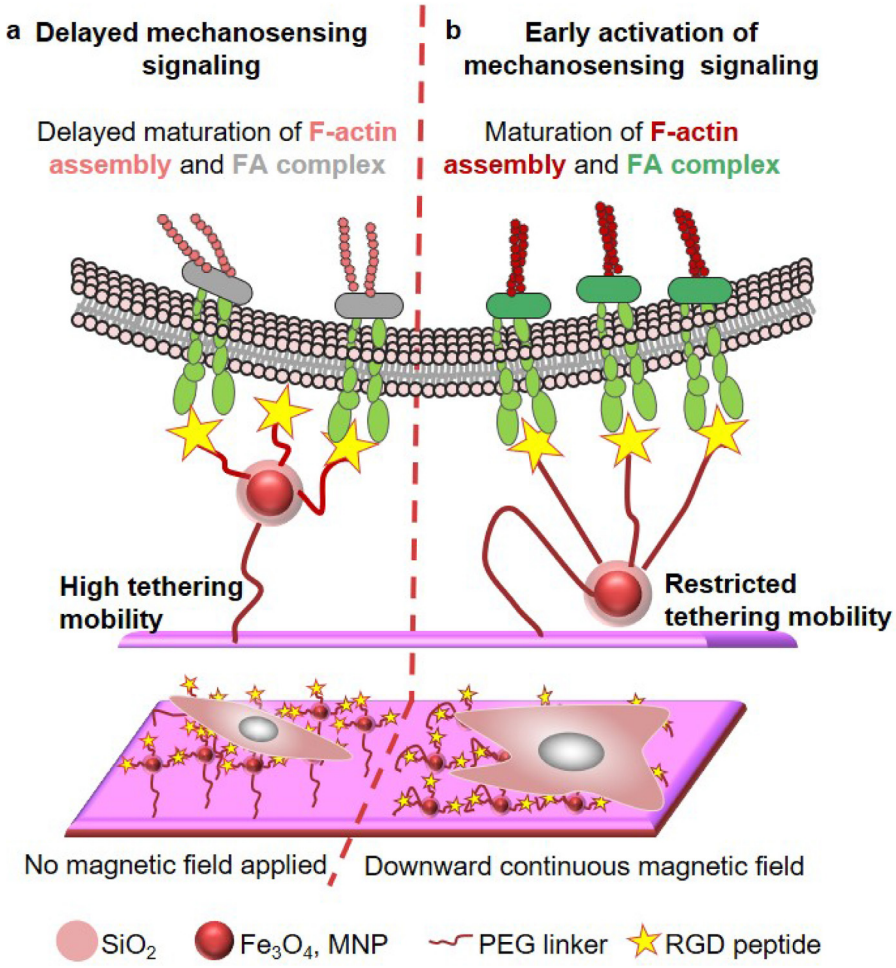

Fig. 8. The tethering mobility of the RGD-grafted magnetic nanoparticle (MNP) substrate can be controlled by the magnetic field to regulate human mesenchymal stem cell behavior [118]. (a) Without the magnetic field, a high tether mobility of RGD-bearing MNPs leads to delayed maturation of focal adhesion (FA) complexes and F-actin filament assembly. (b) With the continuous magnetic field, the tether mobility of RGD-bearing MNPs is restricted that leads to normal maturation of FA complexes and F-actin filament assembly. PEG, poly(ethylene glycol); RGD, arginylglycylaspartic acid.

When external forces were applied to the biological environment, many proteins presented their denatured or extended ability for exposing the specific active peptide sequences to involve in mechanotransduction processes [116]. To mimic the natural mechanotransductive process, a nanoarchitecture of polyelectrolyte multilayers was developed by layer-by-layer self-assembly of $(PLL/HA)_n$ (PLL: poly-(L-lysine), HA: hyaluronic acid) and $(PDADMA/PSS)_m$ (PDADMA: poly(-diallyldimethylammonium), PSS, poly(sodium 4-styrenesulphonate)) as reported by Mertz et al [117] (Fig. 7). The first $(PLL/HA)_n$ polyelectrolyte multilayer is used as a reservoir for loading with enzymes, and the second $(PDADMA/PSS)_m$ polyelectrolyte multilayer is used as a mechanically sensitive capping barrier. The biocatalytic activity of the film is switched on/off reversibly by mechanical stretching, which exposes enzymes through the capping barrier, similar to the mechanisms involved in proteins during mechanotransduction. The designed mechanotransductive surfaces enable to induce the biochemical reactions (activating specific signaling pathways or biocatalytic progress) by mechanical stress. Cellular adhesion triggered cell function also could be tuned by stretching when adhesion ligands such as RGD instead of enzymes.

5. Other stimuli

Similarly, the other stimuli such as magnetic and thermal stimuli have been used for the regulation of living cells. These stimuli often modulate materials' environment that contacts with living cells.

Controlling surface conjugation of tethered cell-adhesive anchorage (e.g. Arg-Gly-Asp/RGD peptide) on non–cell-adhesive substrates is critical to regulate cell function. There is a highly desirable need for a direct, physical, and tether controllable substrate to minimize other potential interferences on cells for modulating the tethered cell-adhesive motifs and controlling the cell adhesion behavior. Wong et al [118] developed a new substrate to tune the tether mobility of RGD on the substrate via magnetic force (Fig. 8). They conjugated a monolayer of RGD-grafted magnetic nanoparticles on glass substrates using the PEG linker (average molecular weight (MW): 2000). The large molecular weight of PEG with the flexible and coiled properties can increase RGD tether mobility. By applying magnetic attraction on magnetic nanoparticles, the RGD tether mobility is significantly reduced. Human mesenchymal stem cells show significantly better adhesion, spreading, and osteogenic differentiation on restricted RGD tether mobility substrates than the high RGD tether mobility substrates. This work not only highlights the influence of the dynamically presented cell-adhesive motifs on cellular behaviors and functions but also presents a potent non-contact strategy for further investigating mechanobiological mechanisms of cellular responses.

The magnetic response provides a high potential strategy for temporally and remotely manipulating cellular functions *in vivo* owing to the excellent penetration with minimal cytotoxicity. Therefore, Kang et al [119] also developed magnetic responsible and reversible uncaging and caging of nanoparticle-bearing RGD-based biomaterials for *in vivo* applications based on deep and safe tissue penetration (Fig. 9). They designed and constructed a magnetic heterodimer that conjugated magnetic nanoparticles as nanocages to the underlying RGD-decorated gold nanoparticle by a flexible and coiled long thiol-PEG linker. This magnetic nanocage(-gold nanoparticle-RGD) heterodimer can be used as a magnetic nanoswitch to reversibly and efficiently regulate nanoscale RGD presentation, thereby controlling stem cell adhesion and spreading, both *in vitro* and *in vivo*. Physical, non-invasive, tissue-penetrative,

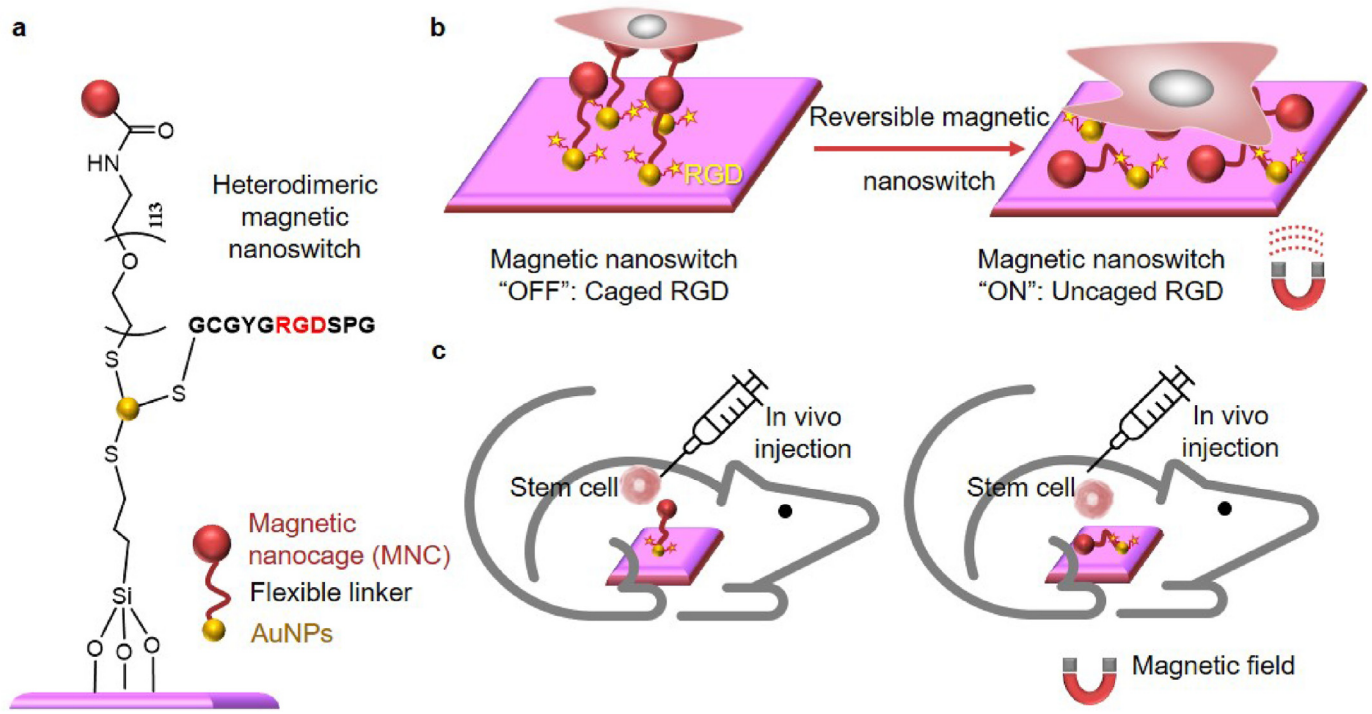

Fig. 9. The heterodimeric magnetic nanoswitch consists of the magnetic nanocage (MNC) grafted to RGD motif–bearing gold nanoparticle (AuNP) by a flexible PEG linker on a substrate (a) [119]. Based on the remote and temporal penetration of the magnetic field, this MNC-(AuNP-RGD) substrate with the magnetic responsible and reversible properties can regular stem cell adhesion and spreading by blocking or exposing RGD, both *in vitro* (b) and *in vivo* (c). PEG, poly(ethylene glycol); RGD, arginylglycylaspartic acid; NP, nanoparticle.

biocompatible, and reversible uncaging of RGD motifs by heterodimeric magnetic nanoswitches holds a high promise in remote and temporal regulation of cell behavior and function for *in vivo* applications.

Cells are surrounded by dynamically extracellular matrices that are composed of fibrous cellular matrices with the micrometer-scale diameter *in vivo*. Thus, it is particularly important to develop a

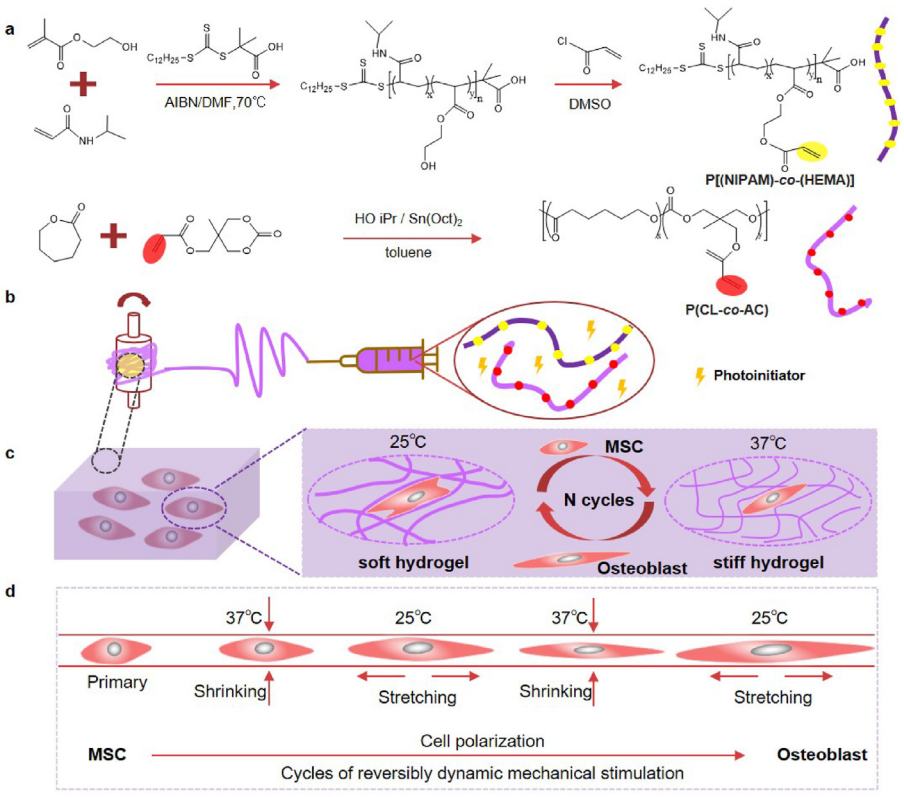

Fig. 10. (a) Synthesis of P[(NIPAM)-co-(HEMA)] and P(CL-co-AC) [120]. The functional groups of acrylate are labeled in yellow or red. (b) P[(NIPAM)-co-(HEMA)] and P(CL-co-AC) mixed with a photoinitiator and electrospun onto the collector. The microfibrous networks were formed after photo-crosslinking. (c) The osteogenic differentiation of human mesenchymal stem cells (hMSCs) can be induced by the multiple cycles of reversible mechanical stimulation based on the temperature alternations between of 25 °C and 37 °C. (d) The microfibrous structure with dynamic and reversible mechanical changes regulates hMSC behaviors and fate correlating to the cell polarization process. P[(NIPAM)-co-(HEMA)], poly(-*N-isopropylacrylamide-co-2hydroxyethyl methacrylate)*; DMSO; dimethyl sulfoxide, AIBN; azobis(isobutyronitrile) , DMF; N,N-dimethylformamide.

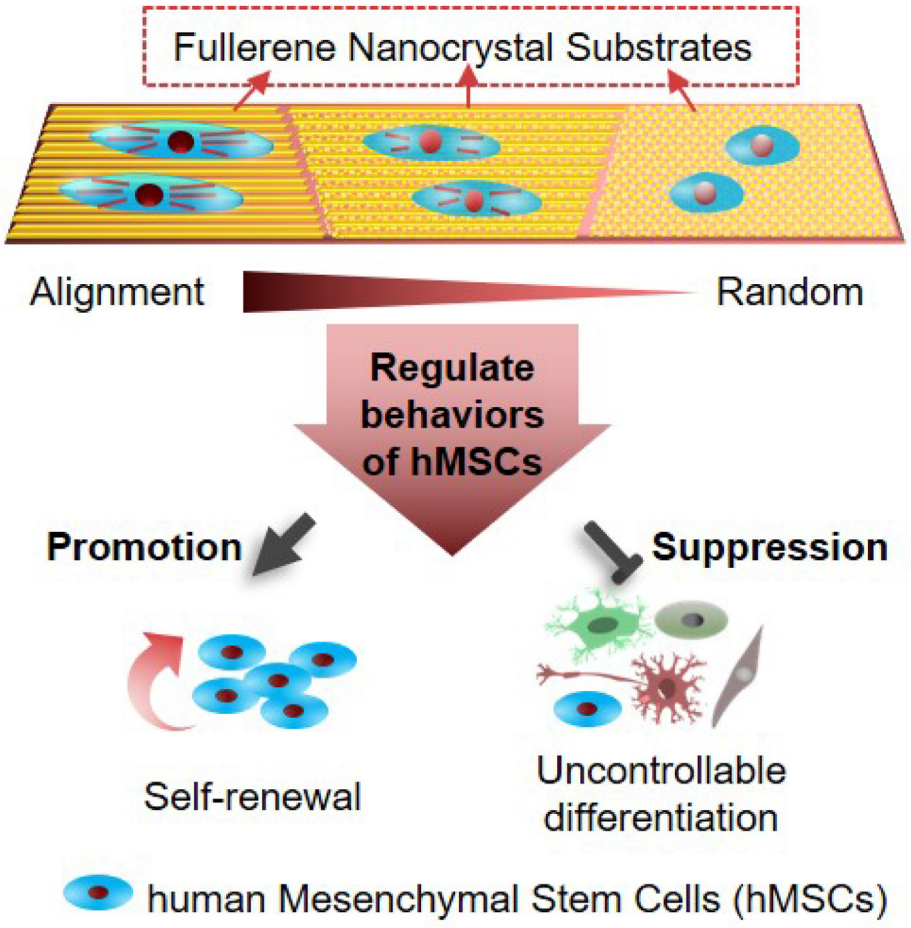

Fig. 11. Aligned fullerene nanocrystal substrates for human mesenchymal stem cell expansion with the maintenance of multipotency *in vitro* [147].

reversibly dynamic mechanical stimulation of three-dimensional microfibrous scaffolds to mimic the natural microenvironment to regulate the responses of cells. Zhang et al [120] designed and constructed thermosensitive electrospun microfibrous hydrogels by covalently cross-linking of polycaprolactone (PCL) and poly(*N*-isopropylacrylamide) (Fig. 10). The mechanosensing of stem cells is in situ thermoinduced switched from stiff (37 °C) to soft (25 °C) for multiple cycles. The deswollen (stiff) states at 37 °C of the hydrogel prefer to generate mechanical deformation, which can promote cytoskeleton rearrangements. The swollen (soft) states at 25 °C of the hydrogel induce physical stretching, which can promote focal adhesion elongation of the cell. Multicyclic reversible dynamic mechanical stimulation results in an increase of human mesenchymal stem cell spreading, adhesion, nuclear translocation of Yes-associated protein signaling molecules, and osteogenic differentiation compared with the cell cultured under normal conditions. Such a cellular response enhances mechanical feedback by dynamic mechanical interactions of cells and the three-dimensional fibrous architecture, which provides an important platform to explore the mechanics of cellular behavior in tissue engineering.

It is still largely unknown how the dynamic cues influence stem-cell spheroids' fate within three-dimensional soft microniches. Zhang et al [121] prepared thermoresponsive stiffness cyclable hydrogels by embedding photocrosslinkable gelatin methacryloyl hydrogels in stimulus-responsive poly(*N*-isopropylacrylamide-co-2hydroxyethyl methacrylate) nanogels. Multicyclic altering of the temperature from 25 to 37 °C and viscosity changes of hydrogels dynamically alter the overall reaction force that stem cell spheroids can control the spreading and adhesion in soft microniches. Moreover, these dynamic cell culture systems can regulate the stem cell spheroid differentiation to osteogenesis in soft microniches by enhancing the maturation of focal adhesin complexes, upregulating the nucleus translocation of the biochemical signal Yes-associated protein, and increasing the expression of lamin A/C. In converse, without multicyclic altering of the temperature, the different viscosities of hydrogels have a negligible influence on the spreading of human mesenchymal stem cell spheroids under static culture conditions.

Uto et al [122] precisely designed nanoarchitectures by cross-linking PCL macromonomers. The PCL hydrogel has the shape-memory property with switching of temperature around a biologically related temperature. In addition, this PCL hydrogel presents a suitable surface wettability as the cell culture substrate. Surface topographic and bulk dimensional alterations were spontaneously generated by simple stretching the PCL hydrogel without other complicated fabrication processes. The surface topographical features completely switched from the wrinkled surface to the smooth surface, whereas the bulk dimensional deformation remains initially fixed station via changing the temperature from 32 °C to 37 °C. This shape-memory PCL hydrogel was used to investigate the effects of spatiotemporally presented mechanostructural stimuli on cell alignment. They find that topographical changes drive cell alignment with lower fixed strain, whereas dimensional changes drive cell alignment with higher fixed strain. The temperature-responsive shape-memory materials would become powerful tools for further investigating spatiotemporal regulation of mechanostructural stimuli to control cell fate. In the other examples, thermal treatments are widely used for cell regulations. For

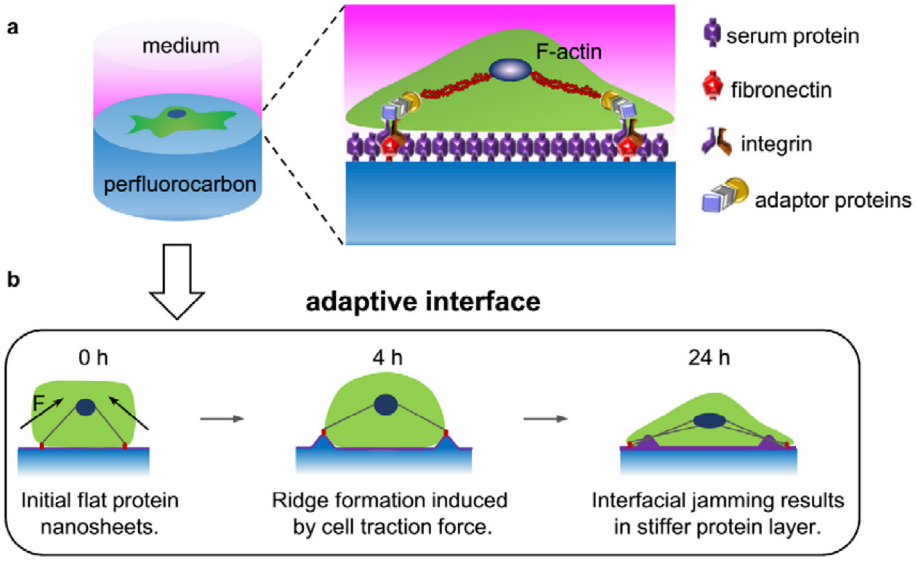

Fig. 12. (a) The fibronectin-integrin-F-actin molecular clutch model for human mesenchymal stem cell spreading at a liquid-liquid interface [149] and (b) the proposed model for the mechanism of human mesenchymal stem cell remodeling of the protein nanosheets for irreversible monolayer-to-fiber transition [150].

example, thermally annealed polyelectrolyte multilayers have been used for regulating cell adhesion [123–126].

6. Effect from the interface

As exemplified previously, behaviors of living cells can be regulated through modified interactions with contacting material interfaces in many cases. Even without distinct external inputs such as electronic, photonic, magnetic, and thermal stimuli, living cells feel mechanical properties of contacting surfaces and respond accordingly. Therefore, regulation of living cells and related biosystems by external mechanical factors has been paid much attention, and an active research field, so-called mechanobiology, has also been developed [127,128]. Nanoarchitectonics approaches to fabricate surface structures with nanocomponents [129–132] have certain contributions to these research fields. Although some examples in the previous sections are actually related to interfacial phenomena, sections strongly focused on the interfacial nature had better be separately presented. In the following sections, some examples on controls of living cell fates at hard surfaces and soft interfaces are discussed from our recent research accomplishments. As hard surfaces, the nanoarchitected surface with aligned nanocarbon materials is used for regulation of living cells. In the second section, investigation of the regulation of living cell fates at a liquid-liquid interface as a totally soft, flexible, uniform environment is explained.

6.1. Hard interface

In the following examples, surface aligned arrays of one-dimensional fullerene assemblies, fullerene nanowhiskers, are used as a hard surface for cell culture. Fullerene molecules are zero-dimensional objects with a single-atom component (carbon) that can be regarded as one of the most fundamental units for self-assembled structures. Upon the liquid-liquid interfacial precipitation method, fullerene molecules, allotropes of carbon whose molecule consists of carbon atoms connected by single and double bonds, such as C_{60}, C_{70}, and their modified derivatives, can be assembled into nanostructures and microstructures [133–135] with various shapes including nanowhiskers [136], nanotubes [137], nanorods [138], nanosheets [139,140], microcubes [141,142], and their integrated structures [143,144]. Among them, one-dimensional fullerene nanowhiskers can be easily aligned at the air-water interface and be transferred as their aligned arrays onto a solid surface by Langmuir-Blodgett (LB) technique. With the LB method, an ultrathin film prepared at the air-water interface can be transferred onto a solid surface. Although the fullerene nanowhiskers have one-dimensional structures such as carbon nanotubes, less bioharmful natures are expected on the basis of larger diameters and less aspect ratios for the fullerene nanowhiskers than carbon nanotubes.

Minami et al. [145] examined differentiation of mouse skeletal myoblast C2C12 cells on hard surfaces of aligned fullerene nanowhiskers, which were transferred onto a solid substrate by the LB technique. On the aligned nanowhiskers, elongated morphologies with high aspect ratios of the cells were observed. Grown myoblasts exhibited polygonal shapes on a glass surface and on randomly aligned fullerene nanowhiskers. Fusion indexes of the cells on the aligned fullerene nanowhiskers were higher than those observed on the bare glass surface of cells. Upregulation of the myogenic genes was confirmed, indicating an acceleration of the early and late stages of myogenic differentiation of the cells on the aligned fullerene nanowhiskers. These mechanically hard oriented surfaces significantly affect cell alignment, growth, and differentiation with reasonable biocompatibility. As more advanced controls of cell alignments, Krishnan et al. [146] demonstrated growth of the human osteoblast cell line MG63 on curvature-controlled assemblies of hard fullerene nanowhiskers that were fabricated using a novel method, vortex LB method. Such interfacial nanoarchitectonics would effectively contribute sophisticated architectures of living cells in two-dimensional plane and for three-dimensional organization.

Human mesenchymal stem cell–based therapies provide a great promise in tissue regeneration owing to their multipotency, easy accessibility, and potent immunomodulatory properties. However, therapeutic efficacies based on human mesenchymal stem cells are hindered by the limited volume of cells isolated from human sources for clinical practice. Song et al. [147] prepared large-area user-defined fullerene substrates to study cell-material interactions for human mesenchymal stem cell expansion *in vitro* (Fig. 11). The diverse assembly of fullerene created various building units involving nanostructures to microstructures, which can be used to form different nanopatterned surfaces by the LB approach. Owing to the highly hydrophobic property and the interaction

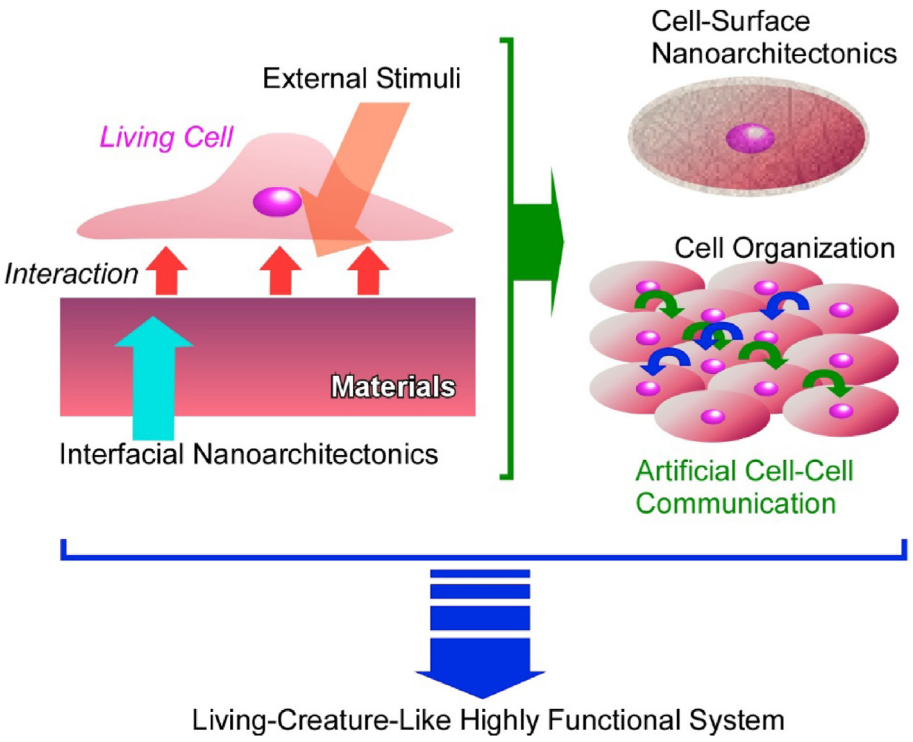

Fig. 13. Plausible future directions to create living creature–like functional systems with the aid of cell controls by interfacial nanoarchitectonics, direct cell surface modifications (cell-surface nanoarchitectonics), cell organization, artificial cell-cell communication, and so on.

with the protein, continuously tunable fullerene-based nanopatterned surfaces were expected to present a controllable cell-extracellular matrix interaction for regulating cell behaviors. They find that the multipotent maintenance with a high proliferation of human mesenchymal stem cells happened on the high aligned fullerene nanowhisker substrate surface. Compared with the flat surface and random fullerene nanowhisker substrates, high aligned fullerene nanowhisker scaffolds provided an appropriate cell contractility to decrease but did not completely disturb mature focal adhesions and polymerized F-actions of human mesenchymal stem cells. The appropriate cell contractility recruited the location of Yes-associated protein from the cytoplasm to the nucleus and then promoted the expression of the stemness genes of human mesenchymal stem cells. Such large-area nanotopographical fullerene substrates for stem cell expansion with maintaining multipotency *in vitro* can improve the potential of stem cell technologies in future tissue-engineering therapies.

6.2. Soft interface

In regular cell culture, living cells are usually grown on solid surfaces such as glass and plastic. Three-dimensional hydrogels that mimic natural tissue are attractive for tissue engineering. People are wondering what stiffness is needed for cells to anchor and spread on the hydrogels. Ultimate softness for cell culture media, liquid-liquid interface can be investigated. In fact, recently, Minami et al. [148] demonstrated successful culture of C2C12 myoblast cells at liquid-liquid interfaces between the aqueous culture medium and perfluorocarbon solvents. Expression of myogenin, myogenic regulatory factors family gene, was significantly suppressed at the examined liquid-liquid interface even when reduction of growth factor levels induced expression of MyoD proteins. Behaviors of the C2C12 myoblast cells at a totally fluidic liquid-liquid interface are significantly different from those observed at the hard interface of fullerene nanowhisker arrays.

Jia et al. [149] have recently showed that a protein monolayer assembled at a perfluorocarbon and aqueous liquid interface can be strong enough for cells to adhere and spread, giving new possibilities for optimizing materials for cell culture (Fig. 12a). The self-assembly behaviors of the proteins at the liquid-liquid interface were tailored by using two different perfluorocarbons: perfluorodecalin and perfluorotributylamine. Compared with perfluorodecalin, proteins at the perfluorotributylamine interface were more significantly denatured and packed more closely, resulting in a stiffer protein monolayer at the interface. With insertion of fibronectin into the protein monolayer, they observed that human mesenchymal stem cells exhibited a greater spread area and larger focal adhesion patches at the perfluorotributylamine interface. At the perfluorodecalin interface, the protein monolayer, which is more pliable, cannot resist the cell traction force and prevents focal adhesion growth and cell spreading. This study suggests that cells do not directly sense the bulk stiffness of perfluorocarbon liquid, but the nanometer level of protein nanosheets at the liquid interface. Therefore, the biomaterial design can be decoupled of bulk mechanical properties from those at local levels. It can be considered to attach a stable protein monolayer to the surface of biomaterials to enable cell adhesion and spreading.

Stem cells have mutual cooperative interactions with their underlying substrates, which is responsible for the regulation of stem cell behaviors and fates. Cell traction forces can rearrange the morphology and stiffness of the extracellular matrix microenvironment. The remodeling of the extracellular matrix can result in feedback to modulate stem cell behaviors and fates. The currently available dynamic biomaterials largely rely on an external stimulus–triggered two-state switching of the presentation and removal of cell-adhesive bioactive motifs. This falls far short of the dynamic adaptive activities occurring between the native extracellular matrix and cells, which can continuously mutually adapt to the other. Liquid can flow and reconfigure its shape to the container. This provides a unique responsive mechanism that is not possible in their solid counterparts. Jia et al. [150] have presented a conceptually new adaptive biomaterial based on a protein monolayer assembled at a liquid-liquid interface (Fig. 12b). Protein assemblies at a liquid-liquid interface adapt dynamically to cell-generated forces by interfacial jamming and nanoscale spatial rearrangement. The elongated fibronectin assemblies in turn promote the elongated focal adhesion, increase focal adhesion

kinase activation, and enhance neuronal differentiation. This provides new scenarios for the elucidation of the feedback mechanisms connecting extracellular matrix dynamic mechanics, biological signaling, and long-term stem cell fate. The ability to enhance neuronal differentiation of human mesenchymal stem cells in the absence of expensive growth factors or complex fabrication procedures represents a significant advance in the field of neuronal tissue engineering.

7. Perspective

Living cells with multitalented capabilities can be regarded as highly advanced stimulus-responsive material systems. Incredibly, they are formed through the spontaneous self-organization of numerous kinds of molecular functional units. Therefore, living cells and related bio-organisms can be regarded as ultimately well-prepared products of nano-architectonics. Fabrication of high functional living cell–like systems is one of the final goals for materials nanoarchitectonics, whereas this target is quite tough in the current level of technology. Instead of preparing the whole cell–equivalent structures from molecular bottoms, integration and fusion of actual living cells and nanoarchitected artificial structures into the stimulus-responsive system is currently an accomplishable approach.

As per these dreams and realities, nanoarchitectonics approaches for responsive cellular biosystems upon various external stimuli including electronic, photonic, mechanical, thermal, and magnetic inputs are discussed in this short review through the explanation of several examples. In many cases, interactions from material surfaces to the cell surface are crucial. Living cells and artificial material systems can communicate with each other through their interfacial contacts. Even without additional external stimuli, the mechanical properties of material surfaces can determine cell fate only through surface contacts. Intelligent mechanisms from the cell surface into the nuclei can be triggered with appropriate stimulation upon contact with nanoarchitected interfaces. We can switch on sophisticated mechanisms of living cells from the cell surfaces.

Based on these features, possible future directions of nanoarchitectonics research for responsive cellular biosystems are briefly described here (Fig. 13). Responsive cellular biosystems should not remain at a single cellular level, and relayed and sequential response in cell organization becomes important targets. The first step would be direct modification of cell surfaces. In fact, the covering and decoration of the cell surface by layer-by-layer assembly has been researched by Fakhrullin et al [151] who named the decorated living cells as cyborg cells. Recently, Shields et al. [152] proposed the cellular backpack strategy to attach an engineered particle to macrophage surfaces for regulation of cellular phenotypes *in vivo*. Well-considered nanoarchitectonics modification of the cell surface leads to living cell systems with responding capabilities to designed external stimuli. In another direction, the construction of cell organization with artificial cell-cell communication is an attractive approach to make multicellular functional systems. Cell assembling methods were already established as seen in cell sheet technology by Nagase et al [153] and Kobayashi and Okano [154]. Nanoarchitectonics essence can be introduced to intercell spaces within cell assemblies to produce artificial cell-cell communication for the cell-to-cell functional relations. In addition, material developments for nanoarchitected platforms for cell adhesion such as self-assembled phosphate-polyamine networks [155] and biocompatible polymer brushes [156–158] have been continuously researched. These efforts would bring us much closer to the final goals of nanoarchitectonics, the creation of living creature–like functional systems. In addition, more application-oriented directions such as advanced therapeutic approaches [17,159] and medical devices [86,160] have to be included in these nanoarchitectonics developments.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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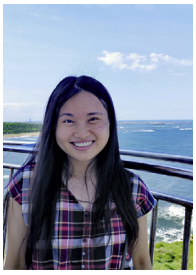
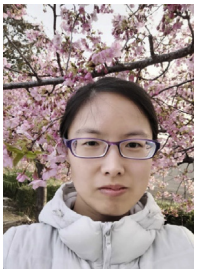


Jingwen Song is a PhD student of The University of Tokyo under the guidance of Professor Katsuhiko Ariga. She is currently studying in the Supermolecules Group at the World Premier International Research Centre for Materials Nanoarchitectonics, NIMS.



Xiaofang Jia received her PhD from Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, in January 2015. Now, she works as a postdoctoral fellow in NIMS.

Katsuhiko Ariga received his PhD from Tokyo Institute of Technology in 1990. He is currently the Leader of the Supermolecules Group and Principal Investigator at the World Premier International Research Centre for Materials Nanoarchitectonics, NIMS. He has also been appointed as a professor at The University of Tokyo.