Remote active control of nanoengineered materials for dynamic nanobiomedical engineering

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Funding information
National Research Foundation of Korea; Korea government, Grant/Award Number: 2020R1C1C1011038; Korea University Grant, Korea University

Abstract
Cells dynamically interact with native nanostructured extracellular matrix at a molecular level in vivo. Developing remotely and actively controllable nanoengineered biomaterials can manipulate and unravel complex cell-material interactions that dynamically occur in the nanoscale in vivo. In this review, we discuss emerging advances in a myriad of recent nanoengineering technologies to design remotely manipulable materials that enable dynamic nanobiomedical engineering at the molecular level. In particular, we focus on remote active stimuli, such as magnetic fields, light, in situ self-assembly, and ultrasound, to manipulate dynamic cell-material interactions in both in vitro and in vivo settings. Remote active control can be particularly appealing with targeting capability for particular locations at any prescribed time points with a degree of reversibility. The unique remote controllability enables the regulation of cellular signaling, adhesion, differentiation, and polarization; cell, drug, and gene delivery; and in situ self-assembly. These materials allow the remote control in regenerative medicine, immunotherapy, cancer therapy, and biocatalysis as well as mechanistic studies on dynamic nanoscale cell-material interactions. We also highlight current challenges in the remote active control, such as reproducibility, tissue-penetrative capability, noninvasive surgery, spatial localization, and temporal variation. Albeit remotely and actively controllable nanoengineered biomaterials are in the nascent stage of development, they can evolve into multiresponsive, reversible, and cost-effective three-dimensional systems with safe and convenient long-term control at the cell, tissue, and organ level toward clinical patient-tailorable on-demand therapy.

KEYWORDS
dynamic nanobiomedical engineering, magnetic control, nanoengineered biomaterial, photonic control, remote active control, self-assembly-based control
INTRODUCTION

In clinical therapy, the modalities for the treatment of a myriad of diseases and trauma demand more convenient, safe, site-specific, and on-demand methods to benefit clinical practices in healthcare systems for both patients and clinicians. Despite these tremendous demands, precisely controlling disease treatment with such innovative methods remains a significant challenge. This is largely due to dynamic changes that occur in the interactions between host cells and the native nanostructured extracellular matrix (ECM) at the molecular level, which arise at disease or trauma sites either locally or systemically. Tremendous advancements in the development of nanoengineering technologies and biomaterials over the past decades have benefited the design of uniquely nanoengineered ECM-emulating biomaterials that can be remotely and actively controlled. These advanced materials can manipulate and elucidate intricate cell-material interactions, thereby benefiting the advancement of comfortable, nontoxic, and location- and time-regulated personalized therapies.

Although these remotely and actively controllable nanoengineered biomaterials can offer unsurpassed advantages for clinical biomedical therapies (Figure 1), their precise control is limited in various aspects largely owing to the challenges in eliciting the efficient responses of the material implants by remote and active stimuli input. For instance, a magnetic field can be externally applied to reversibly manipulate the motion of magnetic nanoparticles (MNPs) ranging from the nanoscale to the macroscale present in the nanoengineered biomaterials, owing to their superparamagnetism.1–6 The remote control of their motion can offer cytocompatible, noninvasive, site-specific, and on-demand therapies but this requires synchronization of the motion of the superparamagnetic nanoparticles with the applied magnetic field. Light illumination can be spatially localized to precisely and noninvasively activate light-responsive nanostructured materials at specific sites.7–10 However, light, particularly in ultraviolet (UV) and visible region, is readily absorbed by living tissues, thereby yielding low degree of responses in the materials and cytotoxicity. Near-infrared (NIR)

FIGURE 1 Remotely and actively controllable nanoengineered materials for dynamic biomedical engineering. The remote and active stimuli include magnetic field, light, and in situ self-assembly. Representative examples include magnetically controlled macroscale ligand sliding, NIR light-controlled photoswitches, and in situ self-assembly-controlled polymerization. Reprinted with permission.6 Copyright 2020, American Chemical Society. Reprinted with permission.7 Copyright 2013, WILEY-VCH. Reprinted with permission.11 Copyright 2020, AAAS
light can overcome this limitation in tissue-penetrative capability.

In situ self-assembly can be remotely induced via an injection of cytocompatible ligands, precursors, peptides, and ions into the targeted sites.11–13 Multifarious nanoengineered in situ self-assembly can be extracellularly and intracellularly induced in the presence of living cells by exploiting unique and cytocompatible biochemical interactions. Piezoelectricity can be actively induced by externally exerting mechanical stimulation, electrical potential, and ultrasound, which is particularly beneficial in activating electrically excitable tissues, such as the nervous, bone, and muscle tissues. In particular, piezoelectricity can be induced with tissue-penetrative ultrasound stimuli to generate electricity, thereby benefiting the remote active control of dynamic biomedical engineering. Indeed, remote active control offers significant advantages with their targeting capability, on-demand applications, and reversibility range (Figure 1).

Remotely and actively controllable biomaterials present unique opportunities to manipulate and understand dynamic interactions between biomolecules present in living cells and nanostructured materials, which regulate various cellular processes, such as cell signaling,14 adhesion,15 detachment, mechanotransduction, differentiation,16–18 polarization,19 and apoptosis. These regulatory mechanisms can be controlled by ligation-mediated mechanosensing, intracellular and extracellular drug delivery,20 and in situ self-assembly, which enable regenerative therapy, immunomodulatory processes, cancer therapy, and biocatalysis and provide insights into fundamental mechanisms of cell-material interactions from a dynamic and nanoscale perspective. Notably, remote and active controllability in designing materials can be combined to endow them with responsiveness to dual stimuli and enable magnetic resonance (MR), photoluminescence, and ultrasound imaging by using magnetic field, light, and ultrasound stimuli, respectively.

In this review, we discuss recent advances in developing remotely and actively controllable materials by harnessing nanoengineering strategies in design principles, which enable their dynamic nanoscale biomedical engineering. We focus on various nanoengineering design strategies to endow materials with remote and active responsiveness in diverse dimensions utilizing unique material control mechanisms as exemplified in Table 1. The unique control of these materials enables their versatile, widespread, and desirable biomedical applications as well as sheds fundamental insights on the temporal and nanoscale cell-material interactions. Although remote active stimuli present potential applicability toward clinical biomedical therapies, current applications are rather focused on the in vitro setting. Wherever possible, we highlight state-of-the-art technologies and potential hurdles in their in vivo applications. We discuss the advantages and disadvantages of harnessing different kinds of remote active stimuli to tailor the design of materials for eliciting desirable functions in specific nanobiomedical applications. The additional benefits of developing these materials can arise in the utilization of three-dimensional (3D) systems, which can be facilely achieved by collective zero-dimensional (0D) nanoparticles, thereby advancing from cellular-level control to tissue- or organ-level control. In the current state, these remotely and actively manipulable materials lie largely in the proof-of-concept stage. Nonetheless, to fully address complex and unmet clinical challenges, these advanced nanoengineered materials pave the way for simple, safe, site-specific, and on-demand therapies tailored for specific disease conditions of patients.

2 MAGNETIC CONTROL OF DYNAMIC BIOMEDICAL ENGINEERING

When the volume of bulk magnetic materials decreases to nanoscale dimensions typically below 20 nm in diameter for iron oxide nanoparticles, one magnetic domain exists, thereby leading to superparamagnetism.21 In this property, the direction of the magnetic moment is aligned in the same direction, whereas no net magnetic moment exists under no external magnetic field. In this property, there is almost no remanent magnetization in the hysteresis loop after the external magnetic field is removed, which prevents the aggregation of superparamagnetic nanoparticles in a stable colloid, thereby allowing a reversible restoration to the original state. High-intensity magnetic fields have been safely applied to patients in MR imaging in the clinics. Therefore, an external magnetic field can remotely manipulate the motion of the superparamagnetic nanoparticles for biocompatible, tissue-penetrative, reversible, and on-demand applications for the patients.

In this review, we classify magnetic nanoengineered materials based on their dimensions (eg, 0D, one-dimensional [1D], two-dimensional [2D], and 3D) typically composed of collective arrangements of superparamagnetic nanoparticles, which determine the dimensions in their motion in response to an external magnetic field (Figure 2). In our definition, MNP nanoclusters, MNP-internalized individual cell, and heterogeneous MNPs were classified as 0D materials because they can exhibit individual motion in a colloidal state in response to an external magnetic field. Magnetic materials at a high aspect ratio in a colloidal state are classified as 1D materials, which exhibit diverse structures, such as chains and helices. The motion of the MNPs can be
TABLE 1  Summary of remotely and actively controllable nanoengineered materials with unique material control mechanisms for dynamic biomedical engineering. The remote and active stimuli methods include magnetic field, light, in situ self-assembly, and ultrasound. For each stimulus, material design is classified with representative examples of material control mechanisms and dynamic biomedical applications.

| Remote control stimuli method | Material design classification | Material control mechanisms | Examples of applications |
|------------------------------|-------------------------------|----------------------------|-------------------------|
| Magnetic field               | Magnetic 0D materials         | Receptor clustering,1,14,22 ion channel twisting,7 magnetic cell capture,24 rotational motion,27 and biocatalysis28 | Signal transduction,3,14,22 ion channel activation,21 in vivo targeting,16,25 stem cell differentiation,49 hyperthermia treatment,77 and cancer therapy24,28,29 |
| Magnetic 1D materials        | Spontaneous linear assembly and rotational motion4 | Gene delivery,10 in vivo drug delivery, and targeting4 |
| Magnetic 2D materials        | Macroscale sliding,5 nanoscale oscillation,30 and physical uncaging of nano-ligand34 | Mechatronicsensing and stem cell differentiation6,34,38 and in vivo macrophage polarization1,15,33 |
| Magnetic 3D materials        | Reversible stretching of macroporous ferrogel1 and cell aggregates17 | In vivo cell and drug delivery,5 stem cell differentiation,7 and tissue engineering35 |
| Light                        | UV-Vis photoisomerizable materials | Exposure and burial of ligand in polyelectrolyte,44 polymer brush,8,42 ligand oscillation,45 and host-guest interaction-mediated ligand availability43 | Cell adhesion,4,42,44 cell adhesion and release,41 and cell mechanosensing45 |
|                             | UV-based photolabile materials | Polymer cleavage-mediated exposure of buried ligand,47 removal of photolabile group,48 and photocaging group9 | Cell adhesion,47 release and patterning,48 and in vivo cell adhesion9 |
|                             | NIR-based upconversion materials | UV-cleavage of ligand,49 molecular cage,10 and photoisomerization50 by NIR-based upconversion using UCNPs | Cell adhesion and release,49,50 drug delivery,10,51 in vivo stem cell differentiation,10 and cell polarization51 |
|                             | Photothermal materials         | NIR-based heat generation with gold nanorods,51 silver triangles,53 magnetic,54 and NIR-based nanobubble formation55 | Photothermal hyperthermia,51,53,54 photodynamic therapy,59,60 and cell adhesion and release56 |
| In situ self-assembly        | Organometallic complexation     | In situ metal ion-peptide coordination on cell surface69 and metal ion-ligand coordination12 | In vivo cell adhesion and release,12 and in vivo immunoregulation69 |
|                             | Cellular enzyme-regulated self-assembly | In situ polymerization on cell surface65 and enzymatic reaction in the cells13,66,67 or tissues68 | Neuron regulation11 and cancer therapy13,65-68 |
| Ultrasound                   | Piezoelectric materials        | 3D cyclic mechanical stimulation,76 electrical stimulation,77,78 ultrasound stimulation for polymer,79 nanoparticle-laden cells,80 and microswimmers81 | Stem cell differentiation,76,77,78 signal transduction,76,77,78 and cell delivery and differentiation81 |

controlled in 2D arrays by an external magnetic field on the surface of substrate materials. These 2D arrays of the MNPs enable reversible cell adhesion on the substrate surface. The aggregated structure of MNPs within bulk materials and MNP-internalized cells were classified as a 3D material because it can show collective motion in the macroscale in response to an external magnetic field.

2.1  Magnetic 0D materials

MNPs in colloidal states can be nanoclustered in situ as they are bound to cell receptors by an external magnetic field or formed in clusters. MNPs can be internalized into cells for in vivo targeting and cell differentiation. MNPs can be heterogeneously prepared for multimodal imaging and biocatalysis. We categorized the
### FIGURE 2

Magnetic nanoengineered materials based on their dimensions (0D, 1D, 2D, and 3D). They are typically composed of collective arrangements of superparamagnetic nanoparticles, which determine the dimensions in their motion in response to an external magnetic field. Examples include magnetic nanotweezers to induce receptor nanoclustering (0D), magnetic microrobots with rotational capability (1D), macroscale nano-ligand sliding (2D), and macroporous ferrogel to enable macroscale deformation (3D). Reprinted with permission. Copyright 2018, American Chemical Society. Reprinted with permission. Copyright 2010, WILEY-VCH. Reprinted with permission. Copyright 2017, AAAS. Reprinted with permission. Copyright 2020, American Chemical Society. Reprinted with permission.

The above-mentioned multifarious examples include magnetic 0D materials. In early studies, Ingber group utilized superparamagnetic nanoparticles (around 30 nm in size) coated with monovalent ligands to allow their binding to transmembrane receptors of living cells. These cell receptor-bound MNPs were attracted and clustered under an application of external magnetic field to activate intracellular biochemical signaling. In another study, RGD ligand- or antibody-presenting magnetic microparticles were also bound to integrin receptors or ion channels on the cell membranes. An application of the magnetic field allowed the activation of mechanosensitive ion channels or receptor clustering.

Cheon group extensively employed magnetic nanotweezers (MNTs) composed of MNPs and magnetic field generators to interrogate the spatiotemporal manipulation of the nanoscale system.
of cells by developing the MNTs (Figure 2).² MNTs can be designed to deliver temporally controlled mechanical stimulation to targeted biomolecules, thereby exerting pulling, dipole-dipole attraction, and rotational forces to the target cells. For example, antibody-conjugated Zn²⁺-doped MNPs (Ab-Zn-MNP) were designed to bind to Tie2 receptors in living cells (Figure 2).³ Upon an application of the external magnetic field, the magnetization of Ab-Zn-MNPs was saturated, which induced strong attractive forces between the dipoles of neighboring MNPs, thereby facilitating the aggregation of the Ab-Zn-MNPs. This magnetically induced nanoclustering of the Ab-Zn-MNPs stimulated multiple signal transduction. Recently, MNPs were coated with antibody targeting deleted in colorectal cancer (DCC) receptor (DCC-MNPs) to bind to neuronal cells. Magnetically triggered DCC-MNP clustering induced neurite extension to connect to preexisting neurons.¹⁴ Magnetic microbeads were coated with antibody to bind to glycoprotein typically expressed by circulating tumor cells.²⁴ A flexible magnetic wire composed of arrays of magnets with alternating polarity, which are covered with polymer catheter, was able to collect the magnetic microbead-captured circulating tumor cells due to the magnetic attraction between the wire and the microbeads.

Instead of the MNPs binding to the cell surface receptors, the MNPs were loaded into cells and an external magnetic field remotely facilitated the targeting of the MNP-loaded cells to stent wires in vivo.²⁵ An external magnetic field generated strong mechanical forces of the zinc-doped ferrite MNP-loaded neural stem cells to overcome steric hindrances for targeting the brain tissues and promoted their neuronal differentiation in vivo.¹⁶ In a different approach, supramolecular self-assembly of the MNPs was demonstrated through the coupling interactions of adamantane and β-cyclodextrin utilizing adamantine-grafted polyamidoamine dendrimers, polyethylene glycol, and MNPs and β-cyclodextrin-grafted branched polyethyleneimine.²⁶ In another study, an application of an alternating magnetic field led to heat generation, thereby facilitating drug release along with MR imaging. Similarly, serum albumin coating-mediated assembly of magnetic nanocubes enabled magnetic cancer hyperthermia.²⁷ Heterogeneous MNPs were designed to realize magnetic field-mediated biocatalytic reactions and drug delivery. Two different MNPs coated with silica were prepared after coupling polyacrylic acid carrying either enzyme or substrate, respectively.²⁸ Janus heterogeneous structure was designed to include MNP-loaded poly(lactide-co-glycolic acid) compartment and poly(caprolactone) compartment.²⁹ Exploiting unique heterogeneous structure, alternating magnetic field was able to induce rotational motion of the Janus microcarriers, thereby enabling co-delivery of dual hydrophobic and hydrophilic drugs along with MR imaging.

### 2.2 Magnetic 1D materials

Magnetic materials can be designed to exhibit 1D diverse structures with high aspect ratio in a colloidal state, such as chains and helices. These unique 1D nanostructures can offer significant advantages in promoting cellular uptake efficiency and sensitivity in MR imaging as well as magnetic field-mediated control of rotational and translational motion of the magnetic materials to accelerate drug release with possible structural disassembly. Recently, ferrimagnetic iron oxide nanocubes (FIONs) were used due to their spontaneous assembly into magnetosome-like 1D ferrimagnetic iron oxide nanochains (MFIONS) via permanent magnetic dipole interactions of the FIONs.³⁰ The MFIONS were further coated with poly(ethylenimine) and plasmid DNA through electrostatic interactions, which exhibited efficient cellular uptake for gene delivery and sensitive MR imaging of the MFION-internalized cells. In addition to chain-like magnetic 1D nanostructures, micro- or nanorobots in 1D hollow helical structures were fabricated.³¹ This helical structure was fabricated via biotemplating synthesis using helical microorganisms to coat the surface with MNPs (Figure 2). Interestingly, this unique helical structure imparted the rotational and translational capability to the magnetic materials under an application of either homogeneously rotating or periodically varying magnetic fields. The magnetic field-controlled motion of the helical materials stimulated targeted drug release along with MR imaging capability in vivo. Furthermore, an application of the ultrasound facilitated structural disassembly of the helical materials into individual 0D nanoparticles.

### 2.3 Magnetic 2D materials

In contrast to previous examples of utilizing a magnetic field to activate freely movable 0D or 1D magnetic nanomaterials in colloidal states, the motion of MNPs can be controlled by an external magnetic field in 2D arrays on the surface of substrate materials. This 2D configurable manipulation of magnetic nanomaterials offers attractive advantages in regulating reversible cell adhesion, mechanotransduction, differentiation, and polarization. In early studies, Ingber group showed that RGD ligand-coated magnetic microbeads can simply be pulled close to the surface of the micropatterned substrate by an external magnetic field to facilitate cell attachment.³² In this system, when the microbeads were pulled off upon
the removal of the magnetic field, cells underwent an apoptosis.

More recently, superparamagnetic nanoparticles have been grafted to the surface of substrate via various physical and chemical coupling mechanisms to remotely control the dynamic presentation of RGD ligand coated on the surface of nanomaterials by an external magnetic field. For example, utilizing an external magnetic field, the planar movement of the ligand-bearing MNPs was remotely controlled to regulate reversible cell adhesion in the macroscale (Figure 2). Specifically, slidable was remotely controlled to regulate reversible cell adhesion on the surface of implants in vivo. In another study, the MNPs were chemically coupled to the surface of the substrate via a flexible PEG linker. The negatively charged slidable MNPs were electrostatically coupled to positively charged surface of the substrate. The 2D sliding of the ligand-bearing MNPs on the surface of the substrate was remotely manipulated by an external magnetic field to regulate macroscale ligand density. Furthermore, this remote regulation of the macroscale ligand density was also effective on the surface of implants to consequentially alter heterogeneous cell adhesion at the macroscale in vivo.

In addition to such physical coupling mechanism, ligand-presenting MNPs were chemically coupled to the substrate surface via a flexible PEG linker. The use of the flexible PEG linker (5000 Da) allowed the ligand-presenting MNPs to exhibit nanoscale oscillations under an oscillating magnetic field. In situ magnetic scanning transmission electron microscopy and atomic force microscopy imaging were used to characterize the nanoscale motion (around 10 nm) of the RGD ligand-bearing MNPs, which is similar to the size of integrin, the receptor of the RGD ligand. Tuning frequencies of the oscillating magnetic field enabled the remote manipulation for the frequencies (0.1-2 Hz) of the nanoscale oscillations of the ligand-presenting MNPs. The device setup to tune the oscillation frequencies of the magnetic field allowed the temporal regulation of host cell adhesion on the surface of implants in vivo. In another study, gold nanoparticles (AuNPs) were first grafted to the substrate surface, which were coated with the RGD ligand. MNPs were subsequently coupled to the surface of the AuNPs via a flexible PEG linker (5000 Da). In this heterodimeric nanostructure design, the MNPs in larger size served as physical magnetic nanocages (MNCs) of the ligand-bearing AuNPs in smaller size. An application of the magnetic field resulted in pulling the MNCs away from the ligand-bearing AuNPs to make the ligand accessible to cells. The removal of the magnetic field resulted in MNCs to revert to caging the underlying ligand-bearing AuNPs, which makes the ligand inaccessible to cells. Owing to highly tissue-penetrable nature of the magnetic field, this reversible physical nanocaging of the ligand was shown to regulate cell adhesion on the implants in vivo.

2.4 Magnetic 3D materials

To exhibit collective motion of the MNPs at the macroscale, MNPs can be aggregated within 3D bulk materials or can be internalized into cells whose 3D aggregation can be induced by applying an external magnetic field. Tremendous efforts have been made in the development of macroporous biomaterials for decades to mediate the release of biological agents from the materials via molecular diffusion, material degradation, cell migration, and others. Utilizing MNP-embedded microporous biomaterials, remote control of the collective motion of the MNPs by an external magnetic field was demonstrated. Mooney group utilized RGD-coupled alginate to fabricate the MNP-embedded macroporous ferrogel that can exhibit large deformation and volume change of over 70% under a magnetic field, which concomitantly trigger the release of cells and drugs on demand (Figure 2). Creation of 3D macroscale tissue structure from individual cells and stimulation of their differentiation have been pursued in tissue engineering and regenerative medicine. Recently, an ability to form 3D aggregation of MNP-embedded cells was demonstrated with a magnetic microtip. Furthermore, the aggregated MNP-embedded cells were sandwiched between two magnetic microtips and mechanical movement of one of the magnetic microtips was able to remotely control cyclic stretching and compression of the aggregated MNP-embedded cells and their differentiation. In another study, the MNP-embedded cells were also magnetically guided to engineer differently shaped tissues by exploiting differently shaped magnet, such as ring, two parallel, and circular magnets.

2.5 Magnetic control of cellular signaling, adhesion, mechanosensing, and function

Dynamic changes occur in the interactions between host cells and the native nanostructured ECM at the molecular level, including disease and trauma sites either locally or systemically. Remote and active control of nanoengineered materials can control and unravel complex cell-material interactions, which can accelerate the development of location- and time-regulated personalized therapies. Magnetic control of the MNPs can govern cell-material interactions at the molecular level to regulate cellular signaling, adhesion, mechanosensing, and function (Figure 3). In particular, dynamic integrin-ligand binding
forms a direct mechanical link between cells and the ECM to regulate structure and contractility of cytoskeleton in a myriad of cells, including stem cells and immune cells. The integrin ligation-mediated mechanotransduction process takes place at the cytoplasm via actin flow, which regulates mechanoresponsive molecules, such as focal adhesion kinase (FAK), rho-associated protein kinase (ROCK), and YAP/TAZ mechanosensitive transcriptional factors, and involves adaptor proteins such as talin, vinculin, and paxillin building focal adhesion complexes.

When cells sense substrate mechanics, integrins and adaptive signaling proteins (that regulate the binding of integrins) link filamentous actin to the substrate. The actin polymerization is enhanced by the transferred mechanical forces, which assist cellular adhesion and downstream signaling. When integrin mediates actin polymerization, actomyosins form actin-myosin complex where myosin motors pull actins to mediate cellular contraction and expansion that regulate cell motility (eg, cell migration and ECM remodeling). YAP/TAZ functions as a vital...
mechanotransducing hub that assists the integration of cellular and tissue mechanics with mechanical and biochemical signaling, which appear in various cell types to regulate mechanotransduction-mediated functional cell differentiation, such as stem cell differentiation.

Similar to stem cells, cytoskeletal dynamics, such as contractile forces produced by F-actin and myosin, play a significant function in cell adhesion and spreading, such as immune cells altering their morphology to mediate their cellular functions. For instance, the shape of macrophages closely regulates immunological macrophage phenotypes. The binding of integrin to RGD ligand on the substrate in macrophages mediates actin polymerization involving an assembly of adaptive proteins, actin, and myosin. These mechanical senses are transferred in the cytoplasm and nucleus via integrins, adaptive proteins, myosin motors, and actins complexes, which are converted into biological signaling pathways to induce cellular responses, such as growth, adhesion, and functional polarization of macrophages.

MNPs coated with monovalent ligands bound to transmembrane receptors of living cells were magnetically attracted and clustered to activate intracellular calcium signal transduction.\(^{22}\) This magnetic nanoclustering triggered a rapid increase in intracellular calcium due to influx from the extracellular environment and intracellular release, which mediate vesicle degranulation and histamine release, thereby initiating local inflammatory response. In another study, integrin receptors or ion channels on the cell membranes were bound to RGD ligand- or antibody-coated magnetic microparticles to magnetically activate mechanosensitive ion channels via twisting magnetic field or receptor clustering to facilitate intracellular signaling.\(^{23}\) Also, antibody-conjugated MNPs bound to Tie2 receptors in the cells were magnetically clustered to facilitate multiple signal transduction for mediating angiogenic processes. Recently, DCC-MNPs bound to neuronal cells magnetically facilitated the receptor clustering (Figure 3).\(^{14}\) This clustering induced functional axonal outgrowth of neuronal cells.

Magnetic control of the motion of the MNPs offers unique advantages in manipulating and understanding dynamic integrin-ligand binding that regulates subsequent signaling pathways. Recently, negatively charged slidable MNPs were electrostatically coupled to positively charged surface of the substrate to magnetically control 2D sliding of the ligand-bearing MNPs on the surface of the substrate to regulate macroscopic ligand density emulating dynamic ECM remodeling.\(^{6}\) This remote regulation of the macroscopic ligand density effectively regulated integrin ligation-mediated activation of mechanotransduction signaling to facilitate osteogenic differentiation of human mesenchymal stem cells (hMSCs) with macroscopic heterogeneity. Specifically, on the magnetically attracted side with high macroscopic ligand density, integrin β1 activation induced stable formation of focal adhesion complexes including FAK and phosphorylated FAK. This activated focal adhesion stimulated Ras homolog family member A (RhoA) to activate ROCK to induce nuclear localization of YAP/TAZ signaling, which facilitated osteogenic differentiation of hMSCs.

Instead of exploiting the macroscopic motion of the MNPs, a recent study utilized nanoscale ligand oscillation (around 10 nm) in diverse oscillation frequencies controlled by the oscillating magnetic field.\(^{38}\) This study was based on the findings that cell adhesion forces on fibronectin- or anti-integrin β1-coated surface exhibited oscillatory cycles at a specific frequency (0.01-0.02 Hz). Interestingly, low frequency (0.02-0.1 Hz) of oscillating magnetic field synchronized with such natural oscillation frequency in cell adhesion significantly facilitated integrin-ligand binding to form focal adhesion complexes to promote adhesion, mechanotransduction, and osteogenic differentiation of hMSCs as compared with high frequency (2-5 Hz) of oscillating magnetic field. The outcomes of this work shed light on the fundamental dynamicity that occurs in cellular adhesion, which can be exploited to fabricate novel dynamic nanoengineered biomaterials. In another study, magnetic control of reversible physical uncaging of ligand-bearing AuNPs dynamically promoted the adhesion, mechanosensing, and differentiation of stem cells, which can potentially assist tissue regeneration (Figure 3).\(^{34}\)

Dynamic magnetic nanoengineered materials were also utilized as implants to study dynamic interactions between host cells and materials. Magnetically controlled 2D sliding of the ligand-bearing MNPs on the surface of implants regulates macroscopic ligand density in vivo.\(^{1}\) Temporally varying heterogeneous ligand distribution regulated the development of adhesion structures of macrophages that modulate their functional polarization phenotypes, which thus spatially and temporally regulated host responses to implants. On the magnetically attracted side in high macroscopic ligand density, macrophages developed adhesion structures with cytoskeletal actin assembly and elongated morphology, which functionally activated their anti-inflammatory and pro-regenerative M2 phenotypes via ROCK signaling. Magnetic control of nanoscale motion speeds of the flexibly coupled ligand-bearing MNPs regulated the adhesion and functional polarization of host macrophages on the implants, which can manipulate host responses to implants, including inflammation or tissue-reparative processes.\(^{33}\) In another study, magnetically controlled uncaging of ligand-presenting AuNPs temporally facilitated the adhesion-dependent M2 polarization of host macrophages involving ROCK signaling.\(^{15}\)
Collective mechanical stimulation can be magnetically induced in three dimensions. Magnetically induced cyclic stretching and compression of the aggregated structure (embryoid bodies) of MNP-loaded embryonic stem cells (ESCs) were sufficient to mediate the differentiation of the ESCs into cardiac pathways through such heart muscle contraction-mimicking cyclic cell stimulation (Figure 3). Stevens group demonstrated that cell orientation can be controlled within 3D hydrogels to engineer various microstructures of cardiac tissues. This study utilized MNP-loaded human cardiomyocytes to orient them by various shapes of the magnet, thereby generating customized, macroscale, and 3D tissue construct, which exhibit normal cardiac function after their grafting onto hearts.

2.6 Magnetic control of targeted cell, drug, and gene delivery, cancer therapy, and biocatalysis

Harnessing magnetic nanostructured materials offers spatial and temporal controllability of the motion of MNPs. Exploiting this unique property, 0D, 1D, and 3D magnetic nanostructured materials enable specific site-targeted and magnetically triggered drug delivery in vivo. In addition, 0D and 1D magnetic nanomaterials can be concomitantly used for MR imaging in diseased sites. Of interests, magnetic micro- or nanorobots in 1D hollow helical structures can load drug molecules into pores and exhibit rotational and translational motion-triggered drug delivery and MR imaging capability in vivo under an application of either homogeneously rotating or periodically varying magnetic fields (Figure 3). This intricate helical structure may potentially access hard-to-reach cavities in the patients. Similar to these microrobots, under an application of alternating magnetic field, the rotational motion of the Janus 0D heterogeneous structure including MNP-loaded and non-MNP-loaded compartments was able to mediate co-delivery of hydrophobic and hydrophilic drugs from each compartment and MR imaging in vivo. This co-delivery allowed the controlled local combination chemotherapy for hepatocellular carcinoma. In other studies, an application of alternating magnetic field yielded heat generation to facilitate drug delivery from self-assembled MNPs or magnetic nanocube assembly-mediated hyperthermia therapy for glioblastoma multiforme tumors along with MR imaging.

Magnetic microbeads coated with antibody were shown to bind to the receptor of tumor cells. By using flexible magnetic wire, magnetic microbead-captured tumor cells were collected from the circulating blood in vivo. Hyeon group demonstrated that 1D ferrimagnetic nanochains can be facilely internalized into MSCs owing to their high-aspect-ratio nanostructure for gene delivery to augment the homing ability of the transplanted MSCs to the ischemic cerebrum. These 1D magnetic chain-loaded MSCs enabled poststroke recovery and MR imaging in vivo. Such cell delivery can be magnetically manipulated to target specific sites in vivo. Zinc-doped ferrite MNP-loaded neural stem cells were magnetically controlled to produce strong mechanical forces to overcome steric barriers in the brain tissues (Figure 3). In addition, they facilitated zinc-mediated Wnt signaling to induce their neuronal differentiation, thereby mediating significant recovery from the brain stroke. Similarly, MNP-loaded endothelial cells were magnetically controlled to target stent wires in arteries.

Intriguingly, harnessing 3D magnetic nanostructured materials can remotely facilitate on-demand delivery of cells and drugs simultaneously in vivo (Figure 3). Magnetic manipulation of the MNP-embedded macroporous ferrogel containing drugs and cells in the macropores facilitated the reversible stretching and compression of the ferrogels and thus released the cells and drugs from the macropores in vivo, thereby enabling the supply of cell sources for tissue engineering applications. Two different heterogeneous MNPs carrying enzyme or substrate, respectively, which were shielded by polymer brushes, were shown to trigger enzymatic reactions by applying an external magnetic field. The merged biocatalytic heterogeneous MNPs liberated the substrate-bound therapeutic drugs as the enzymes degraded the substrate. This magnetic field-mediated biocatalysis enabled drug delivery that effectively inhibited cancer cell proliferation.

3 PHOTONIC CONTROL OF DYNAMIC NANOBIOMEDEDICAL ENGINEERING

Thanks to the widespread availability of photoresponsive molecules and nanoparticles, light illumination can be applied to spatially and temporally activate light-responsive materials including such molecules or nanoparticles. Photoresponsive molecules can be prepared to absorb specific wavelengths of light, typically ranging from UV to visible light, which trigger changes in their chemical structure. Photosomers can be modified to undergo cis-trans isomerization in responses to two different or a single wavelength of light, thereby enabling light-based reversible manipulation. Luminescent nanoparticles, such as quantum dots and upconversion nanoparticles (UCNPs), can be synthesized to absorb and emit specific wavelength of light, typically ranging from UV to NIR light. Photothermal materials can convert NIR light to heat, thereby offering an advantage for hyperthermia therapy. However, NIR can relatively reach deep tissues with less absorption of light. Therefore, an external
light source can remotely activate chemical reactions and associated structural changes of photoresponsive molecules with and without nanoparticles for highly spatial precision, on-demand, and reversible applications.

In this review, we have classified light-responsive nanoengineered materials based on a specific wavelength of light that can remotely control various materials, such as UV-Vis photoisomerizable materials, UV-based photolabile materials, NIR-based upconversion materials, and photothermal materials (Figure 4A-C). Because UV and visible light are readily absorbed by living tissues, photoresponsive materials responding to such wavelength spectra are limited to noninvasive applications in shallow exterior tissues, such as skin and subcutaneous region. UCNPs can be synthesized to absorb NIR light and emit UV or visible light with widespread tunability of such responsive wavelength spectra. Therefore, UCNPs offer a promising strategy to indirectly activate UV- or visible
light-responsive molecules by upconverted light from the NIR illumination. Photothermal materials can also be designed to respond to NIR light. These NIR-responsive materials coupled with upconverted light-responsive molecules offer promising safe applications involving light for the remote control in dynamic biomedical engineering.

3.1 UV-Vis photoisomerizable materials

Photoisomerizable materials utilize photoswitchable molecules, such as azobenzene and spiropyran, which exhibit isomerization-mediated reversible changes in molecular configuration, typically via UV or visible light. For instance, UV irradiation induces trans to cis isomerization of azobenzene, whereas visible light triggers cis to trans isomerization. Spiropyran also undergoes reversible isomerization between closed-ring and open-ring structures under the influence of UV and visible light. Photosomers can be modified to exhibit isomerization by UV-visible light or visible light alone. Photoisomerization can occur directly by UV or visible light illumination or indirectly by NIR-upconverted-UV light or NIR-upconverted-visible light using UCNPs. We first discuss photoisomerizable materials directly controlled by UV or visible light.

Azobenzene has been widely used as a photoswitchable cis-trans isomer possibly due to its simple but facilely modified chemical structure. Azobenzene typically undergoes reversible photoinduced isomerization to the cis state on the exposure to UV light at around 340-380 nm and to the trans state by visible light at around 450-490 nm. However, depending on the modified chemical structure of azobenzene that regulates its energy state, it can be tuned to undergo cis-trans isomerization in response to different wavelength of light. In early work, azobenzene was coupled to alkanethiol and PEG molecule to form self-assembled monolayer on the surface of materials, to which RGD peptide was grafted at the terminal group. Azobenzene grafted to RGD peptide exhibited host-guest complexation to α-cyclodextrin (α-CD) terminal alkanesilane on the surface of materials. In the trans-azobenzene state, RGD-coupled azobenzene and α-CD exhibited host-guest complexation to present RGD in an available form, whereas RGD-coupled azobenzene was dissociated from α-CD in the cis-azobenzene state induced by UV irradiation, thereby releasing the attached cells. In another study, azobenzene was conjugated to polymer as a side chain, to which RGD peptide was coupled in the poly(acrylic acid)-poly(allylamine hydrochloride) polyelectrolyte 2D bilayer on the surface of materials. UV light illumination induced trans to cis isomerization to bury RGD in the polymer layer to modulate cell adhesion.

Recently, the rapid reversible photoswitching of bio-functionalized azobenzene surface was demonstrated (Figure 4A). Azobenzene was functionalized with RGD ligand and coupled to the surface of materials surrounded by PEG brush. Irradiation with UV light at 365 nm for only 20 s rapidly changed the configuration of azobenzene from trans to cis state to bury RGD ligand in the PEG brush, thereby inhibiting cell adhesion. Illumination with visible light at 440 nm switched the azobenzene to the trans configuration to allow the RGD ligand to be available, thereby promoting cell adhesion. Interestingly, azobenzene was modified to carry an electron-withdrawing nitro substituent in one ring and an electron-donating methyl group in the other one. This dipolar substitution pattern induced a red-shift of the π-π* absorption into the visible region to enable a very rapid mechanical oscillation of the azobenzene upon an irradiation with visible light. This configuration of azobenzene, named push-pull azobenzene, was coupled to RGD ligand surrounded by PEG brush on the surface of materials. Visible light-mediated continuous isomerization enabled oscillatory switching of RGD availability from the PEG brush, thereby stimulating cell mechanosensing.

3.2 UV-based photolabile materials

Photolabile molecules are directly cleaved by UV light or indirectly by NIR-upconverted-UV light using UCNPs. We first discuss photolabile molecules directly cleavable by UV light. Photolabile molecules, such as o-nitrobenzyl and related groups, have been widely used as photoremovable protection groups for caged molecules. Photocleavage of these groups activates the caged functional molecules, such as cell-adhesive RGD peptides, at the prescribed time. Photolabile molecules can be coupled on the nanopatterned or nonpatterned 2D surface of materials or hydrogels.

Photoactivatable nanopatterned materials have been prepared by coating the surface of materials with periodically arrayed AuNPs, to which RGD ligand was coupled. The remaining area not covered by RGD-presenting AuNPs was grafted with photocleavable long PEG molecules to bury the RGD-bearing AuNPs. Under UV irradiation, the photocleavage of the long PEG molecules enabled the RGD ligand to be accessible. In another study, an intercalated 4,5-dialkoxy 1-(2-nitrophenyl)-ethyl photocleavable group was also directly conjugated with RGD ligand. UV illumination of this material resulted in direct cleavage of RGD ligand. This approach using UV light was found to be efficient in spatially patterning cells using a photomask by selectively releasing the attached cells. Recently, a photolabile cage that can protect and
activate the RGD peptide was designed with cyclic RGD peptide modified with 3-(4,5-dimethoxy-2-nitrophenyl)-2-butyl ester photolabile caging group on poly(ethylene glycol)-di-acrylate hydrogels (Figure 4B). On exposure to UV light, the caging group was released, thereby resulting in the time-regulated presentation of the active RGD peptide to activate cellular adhesion in vivo.

### 3.3 NIR-based upconversion materials

UV-Vis photoisomerizable and UV-based photolabile materials both require the use of UV and/or visible light for their remotely controlled activation. However, their translational applications in vivo are limited owing to strong absorption of UV and visible light to living tissues, thereby exerting potential cytotoxicity in vivo. Therefore, UCNPs with capability to upconvert tissue-penetrative NIR light to UV and/or visible light are harnessed as an alternative for potential in vivo applications. Lanthanide-doped UCNPs are composed of guest-host components typically including host lattices materials with trivalent lanthanide ions. The dopants of lanthanide act as optically active centers, which generate emission when excited. Owing to the unique energy-level structures of lanthanide ions, UCNPs can absorb NIR light and emit high-energy photons in a wide range of spectra including UV, visible, and NIR region. UCNPs have been used in photoluminescent imaging, NIR-induced mediators for photolysis, and photoswitch of isomers, such as azobenzene and spiropyran molecules. It is worth noting that the efficacy of controlling photoresponsive materials by indirectly upconverted UV or visible light may be lower than that by direct UV or visible light, which necessitates precise synthesis of the UCNPs emitting specific wavelength of upconverted light in high intensity.

The surface of 2D materials was coated with UCNPs, to which UV-cleavable 4-(hydroxymethyl)-3-nitrobenzoic acid molecule, PEG linker, and RGD peptide were sequentially attached. The irradiation of NIR laser at 980 nm to the UCNPs allowed the emission of photons in the UV region to mediate the removal of the UV-cleavable molecule and thus connected RGD peptide. This NIR-controlled activation enabled on-demand release of the attached cells. In another study, UCNP-based photosensitive nanocarrier was also developed by the UCNPs coated with mesoporous silica layer and then coupled with photocleavable linker [4-(8,8-diethoxy-3-oxo-2,9-dioxo-4-aza-8-silaundecyl)-3nitrobenzoic acid] and molecular cage (β-cyclodextrin) (Figure 4C). Calcium chelator or calcium supplier was loaded into mesopores, which were caged by the β-cyclodextrin. This nanocarrier was readily internalized into cells, to which NIR light was illuminated to facilitate NIR-to-UV-upconverted light-mediated photolysis of the linker and connected caging molecule, thereby leading to the intracellular delivery of cargo molecules to regulate cell differentiation or polarization.

The combinational use of photoisomers and UCNPs enables NIR light-controlled reversible photoisomerization. Spiropyran-conjugated multi-shell UCNPs were prepared in 2D array on the surface of materials. At high laser power, the visible light emission from the UCNPs was prominent, which induced the formation of ring-opening merocyanine isomer. At low laser power, the visible light emission from the UCNPs was dominant, which induced the reverse ring-closing process as a spiro form. This spiro form promoted the adsorption of fibronectin to mediate cell adhesion, whereas merocyanine isomer suppressed the adsorption of cell-adhesive protein to induce the release of the attached cells. In another study, NaYF₄:TmYb@NaYF₄ core-shell UCNPs coated with mesoporous silica were used with coupling of photomechanical azobenzene groups to the drug-loaded mesopores of silica, which acted as stirrers in the mesopores (Figure 1). Under irradiation of NIR light at 980 nm, the UCNPs converted NIR light to UV and visible light simultaneously to mediate reversible transition between trans and cis state with continuous rotation-inversion movement, thereby facilitating the release of the loaded drug.

### 3.4 Photothermal materials

Photothermal nanoengineered materials convert photoenergy to heat, which is used for photothermal hyperthermia therapy as well as the regulation of cellular adhesion and release. Various materials that can induce photothermal effect include AuNPs, silver nanoparticles, carbon nanotubes, and magnetite nanoparticles. By tuning the shape and size of such nanomaterials, the efficiency of switching light energy to heat energy changes. Furthermore, gold nanoshells, nanorods, and nanocages with NIR resonant frequency are designed owing to their benefits in clinical therapy due to high tissue-penetrative capability of NIR light. In early studies, gold nanorods were designed to exhibit photothermal effect under an irradiation of NIR light at 800 nm. Gold nanorods coated with growth factor receptor antibodies selectively entered malignant cells to enable NIR-triggered cell destruction. Single-walled...
carbon nanotubes were also developed to enable the destruction of tumor growth in vivo by irradiating NIR light at 808 nm. It was later discovered that silver triangles exhibit superior photothermal hyperthermia to gold nanorods under an irradiation of NIR light at 800 nm. Magnetite nanoparticles were also designed to exhibit spherical, hexagonal, and rod shapes. These uniquely shaped magnetite nanoparticles were loaded into cancer cells to generate heat upon NIR laser irradiation at 808 nm, which effectively damaged cellular organelles.

Hollow gold nanoshells were designed to respond to high-energy (gigawatt level) NIR laser irradiation for a short period of time (nano- to femtoseconds) for yielding bubble formation and liposome rupture, thereby enabling potential photothermal cancer therapy. Photothermal nanoengineered materials were also designed with 2D array of nanomaterials. Plasmonic surface of materials was prepared by utilizing 2D array of AuNP seeds and their anisotropic growth. NIR light irradiation at 980 nm yielded photothermal effect on the gold-nanoengineered surfaces of materials, thereby enabling the release of the attached cells. In another study, photothermal nanoengineered materials were fabricated by using graphene surface modified with gold nanorods, to which RGD-modified dsDNA was coupled. NIR light illumination at 808 nm demonstrated photothermal effect that mediates the disassembly of RGD-modified dsDNA to release the attached cells.

3.5 Photonic control of cell adhesion, release, and patterning

Employing light-controllable materials enables temporal control of the photoactivation on the materials, thereby dynamically regulating cell behaviors, such as cell attachment, detachment, and patterning, which have been typically achieved on 2D surface of materials. Direct use of UV light for photoactivatable nanopatterned materials was demonstrated by burying RGD-coated AuNPs with long UV-cleavable PEG brush. UV light-mediated photocleavage of this brush allowed the RGD ligand to be accessible to cells, thereby temporally mediating cell adhesion and collective cell migration. In another study, UV light was also directly used to cleave and release photolabile group modified with RGD peptide. Using a photomask, this strategy showed an efficacy in spatially patterning cells by selectively releasing the attached cells.

Photoisomers, such as azobenzene derivatives, undergo cis-trans chemical structure changes to reversibly expose RGD ligand linked to azobenzene derivatives, thereby dynamically modulating cell adhesion and release. RGD-modified azobenzene linked to polymer in the polyelectrolyte 2D bilayer on the surface of materials enabled UV light-mediated trans to cis isomerization to bury RGD in the polymer layer to modulate cellular adhesion. In other configuration, RGD-coupled azobenzene in 2D self-assembled monolayer on the surface of materials exhibited visible light-mediated trans isomerization to promote cell adhesion and reversible UV light-induced cis isomerization to suppress cell adhesion. Cell adhesion and release was also shown to be regulated by UV light-mediated trans-to-cis transition of azobenzene. In another study, RGD-coupled azobenzene exhibited reversible host-guest complexation to trans-cis transition of azobenzene was promoted in the trans-azobenzene state via host-guest complexation-mediated RGD presentation. Cellular release was facilitated in the cis-azobenzene state by disrupting host-guest complexation to release RGD. Recently, RGD-coupled azobenzene surrounded by PEG brush on the surface of materials exhibited rapid transition to cis state by short irradiation with UV light at 365 nm to suppress RGD availability for inhibiting cell adhesion (Figure 4A). Conversely, visible light irradiation at 440 nm reverted the azobenzene to trans state to elevate RGD availability for promoting cell adhesion. Intriguingly, using a single wavelength of visible light at 530 nm, RGD-coupled push-pull azobenzene configuration allowed an oscillatory switching of isomeric form. This high-frequency ligand oscillation (10² to 10⁵ Hz) was found to stimulate cell mechanosensing and upregulate the adhesion-associated gene expression.

Garcia group demonstrated that RGD peptide modified with a photolabile caging group on hydrogels allows UV light-controlled photocleavage of the caging group to actively present RGD peptide on 2D surface of materials in vivo (Figure 4B). This pioneering in vivo work enabled the temporal control of in vivo cell adhesion, inflammation, fibrous encapsulation, and vascularization of the subcutaneously implanted materials. Although this work proved an efficient control of such photolabile materials in vivo, the use of UV light to irreversibly activate the materials hampers their translational applications to patients due to potential cytotoxicity of the UV light to living tissues. Indeed, this study showed that the 90% of the illuminated UV light was absorbed by the skin.

To overcome such strong absorption of UV and visible light in vivo, NIR light-responsive UCNPs with UV-cleavable RGD peptide were coated on the surface of 2D materials. In this study, NIR light illumination at 980 nm enabled the irreversible cleavage of RGD peptide via upconverted UV light to release the attached cells at prescribed time. In another study, the combinational use of photoisomers and UCNPs allowed NIR light-controlled reversible photoisomerization to mediate cell adhesion, release, and patterning. Spiropyran-coated multi-shell
UCNPs on 2D array on the surface of materials exhibited cell-repellent and cell-adhesive isomerization by high laser power (8 W/cm²) and low laser power (0.5 W/cm²) of NIR light illumination at 980 nm. This reversible transformation enabled reversible cell adhesion and detachment in repeated cycles. Furthermore, cellular adhesion and release can be controlled by NIR light using photothermal nanoengineered materials in the absence of UCNPs. Photothermal nanoengineered materials were fabricated with 2D array of anisotropic gold nanomaterials. Plasmonic surface of materials was prepared by utilizing 2D array of AuNP seeds and their anisotropic growth. NIR light irradiation at 980 nm to this plasmonic surface of materials produced photothermal effect to mediate the release of the attached cells in high viability for tumoral cells (HeLa and A549) as well as nontumoral human umbilical vein endothelial cells (HUVECs). In another study, photothermal nanoengineered materials were also designed by employing graphene modified with gold nanorods bearing RGD-modified dsDNA. NIR light illumination at 808 nm to this surface of materials generated photothermal effect to direct the disassembly of RGD-modified dsDNA, thereby mediating the release of the attached HUVECs.

### 3.6 Photonic triggering of drug delivery

UCNPs coated with mesoporous silica were used as drug delivery nanocarrier with photoisomer, azobenzene. Anticancer drug was loaded into the mesopores in the silica layer, to which azobenzene was coupled. Under NIR light irradiation at 980 nm, the UCNPs converted it to UV and visible light simultaneously to mediate continuous transformation of azobenzene between cis and trans states, thereby exerting photomechanical movement to trigger the release of the loaded anticancer drug. In a recent study, UCNP-based photoresponsive nanocarrier was employed for NIR light-controlled intracellular drug delivery in vivo (Figure 4C). This nanocarrier was loaded with chondroinductive kartogenin (KGN), calcium chelator, or calcium supplier and their intracellular delivery was regulated by NIR light-mediated photocleavage of caging molecule by upconverted UV light. Intracellular KGN delivery led to the differentiation of transplanted hMSCs into hypertrophic chondrocytes. NIR-regulated intracellular calcium decrease along with KGN delivery directed their differentiation into chondrocytes by suppressing hypertrophy. Conversely, intracellular calcium elevation along with KGN delivery facilitated the differentiation of hMSCs into osteoblasts. This NIR light-mediated regulation of stem cell differentiation was demonstrated with subcutaneously implanted hMSC-laden hydrogel in vivo. In another study, the NIR light-mediated control of intracellular calcium levels efficiently facilitated M1 polarization of macrophages with high intracellular calcium or their M2 polarization with low intracellular calcium.

### 3.7 NIR-controlled photothermal and photodynamic therapy

Various nanoengineered materials have been designed to convert tissue-penetrative NIR light to heat for photothermal hyperthermia therapy. Among such materials, silver triangles exhibited superior photothermal hyperthermia to gold nanorods in human nonsmall lung cancer cells. In another study, NIR light at 808 nm was irradiated into MNP-loaded cancer cells for their photothermal hyperthermia therapy via an effective heat generation to damage cellular organelles, thereby yielding shriveled and disintegrated cells and discontinued and reduced tumor tissue in vivo. Although not investigated in this study, this uniqueness of the MNPs for NIR-responsive photothermal therapy potentially suggests that this approach enables dual NIR- and magnetic field-based remote control of such dynamic therapy.

Photothermal effect can also generate cytotoxic radicals to cause tumor cell death via heat-induced chemical reaction for photodynamic therapy. Initiator-loaded Au nanocages absorb NIR light that induces photothermal effect to decompose the initiator and generate alkyl radicals (R·). The generated alkyl radicals impair DNA to induce the apoptosis of cancer cells. In another study, Fe ion that can catalyze the generation of reactive oxygen species was used for photodynamic therapy. Upon NIR irradiation, an antiferromagnetic pyrite leads to in situ surface oxidation and maintains H₂O₂ disproportionately to catalyze ·OH generation to enable photodynamic therapy, which is further facilitated by heat-induced Fenton process.

### 3.8 X-ray-controlled cancer therapy

Similar to NIR light, X-ray is tissue penetrative and has been utilized to induce chemical reactions for photodynamic therapy. To minimize the dependence on oxygen in the photodynamic therapy, a scintillator and a semiconductor are combined to generate LiYF₄:Ce³⁺@SiO₂@ZnO-PEG nanoparticles (SZNP), which were used as a photosensitizer activated by ionizing radiation. The scintillator of SZNP down-converted X-ray radiation to match the energy gap of semiconductor, which subsequently generated reactive oxygen species from...
water molecules. In another study, sacrificial electron acceptors are used to yield ·OH with high efficiency. Semiconductors can generate electron and hole pairs which, however, readily recombine. A cisplatin prodrug (Pt(IV)) was used to develop LiLuF₄:Ce@SiO₂@Ag₃PO₄@Pt(IV) nanoparticles, which were utilized as a sacrificial electron acceptor to separate the electrons and holes to generate ·OH. Moreover, the cisplatin produced from Pt(IV) elevated DNA damage induced by ·OH, thereby enhancing the efficiency in the photodynamic therapy. Nanoscale metal-organic layers can also generate hydroxyl radicals under X-ray irradiation.

4 | IN SITU SELF-ASSEMBLY- AND DISASSEMBLY-BASED CONTROL OF DYNAMIC NANOBIOメディカル ENGINEERING

Self-assembly process is the spontaneous organization of chemical components into structurally organized aggregates or networks via various interactive mechanisms, such as electrostatics, metal ion-ligand coordination, and enzymatic reactions. In particular, in situ formation of self-assembled nanostructures in the presence of living cells induced by utilizing biochemical reactions of cytocompatible ligands, precursors, peptides, and ions offers a powerful method to remotely and actively control cell-nanomaterial interactions. Therefore, these materials can be remotely controlled in the absence of physical stimuli. In this review, we focus on the remote control of self-assembly-based materials classified into two categories based on material assembly control mechanisms, such as organometallic complexation and cellular enzyme-regulated self-assembly, as well as degradation-inducible nanomaterials.

4.1 | Organometallic complexation

The organometallic complexes are assembled by coordination between metal ions and organic ligands. This coordination is based on their specific and reversible association. The metal ion-peptide-based in situ self-assembly of nanofibers from nanoparticles was induced on the cell surface. Peptide-based building blocks were composed of bispyrene motif, Lys-Leu-Val-Phe-Phe (KLVFF) motif, and RGD. Bispyrene motif formed nanoparticles due to their strong hydrophobicity and π-π stacking. Calcium ions were found to bind to RGD and activated metal ion-dependent adhesion site of integrin, which promoted the binding between peptide-based building blocks and integrin. The KLVFF motif was shown to mediate the formation of nanofibers from the peptide-based building blocks through β-sheet hydrogen bonds, which led to the apoptosis of cancer cells. Recently, metal ions and organic ligands were harnessed to mediate in situ self-assembly of organometallic nanoparticles in the presence of living cells (Figure 5A). Bisphosphonate containing two phosphonate groups was used as organic ligand, which readily coordinates with magnesium metal ions to form 3D network structure with the help of hydrogen bonds. In this study, AuNPs grafted to the surface of materials were coated with bisphosphonate. The bisphosphonate-coated AuNPs facilitated the binding of the magnesium ions to induce self-assembly of nanoparticles on the surface of AuNPs in heterodimeric nanostructure via magnesium ion-bisphosphonate coordination. This self-assembly was versatile because RGD ligands were also able to be incorporated in the self-assembled nanoparticles. Furthermore, this self-assembly was reversible via ethylenediaminetetraacetic acid (EDTA)-mediated chelation of magnesium ions to dissolve the self-assembled nanoparticles. This in situ self-mediated processes enabled the regulation of cell adhesion, release, mechanotransduction, and immunoregulation.

4.2 | Cellular enzyme-regulated self-assembly

Remote control of self-assembly-based materials can be achieved by utilizing cellular enzyme-regulated self-assembly. Electrically functional conductive polymers were synthesized at the plasma membrane of neurons (Figure 5B). The ascorbate peroxidase apex was used to enable polymerization on the cell surface. The supply of conductive polymer precursors and aniline monomer-dimer mixture triggered oxidative radical cation polymerization at the enzyme reactive center. The conductive polymers were synthesized on the cell surface. In addition to the self-assembly on the cell surface, in situ self-assembly was intracellularly induced via cellular enzyme-triggered biochemical reactions. Non-self-assembling precursors are turned into the self-assembling peptides by an enzymatic reaction of carboxylesterases that are highly produced and activated in cancer cells (Figure 5C).

In another study, in situ self-assembly was intracellularly induced by cellular enzyme-triggered gelation using a peptide lipid as a gelator precursor. This gelator precursor formed nanofibers via in situ self-assembly after cleaved by a cancer cell-related enzyme, matrix metalloproteinase-7, thus leading to hydrogelation for cancer therapy. Recently, taxol derivative was designed, which is composed of 2-cyanobenzothiazole.
motif, taxol motif conjugated to the side chain of a lysine motif, disulfide-functionalized cysteine motif, and RVRR substrate. After the cellular uptake of taxol derivative, the trans-Golgi protease furin cleaved taxol derivative to mediate the self-assembly of hydrophobic oligomers into taxol nanoparticles for cancer therapy.\(^{67}\) Recently, a small molecule precursor was designed, which self-assembles into nanofibers via an enzymatic reaction in tumor sites.\(^{68}\) The precursor was composed of purpurin 18 as a functional molecule, Pro-Leu-Gly-Val-Arg-Gly (PLGVRG), as the enzyme-responsive peptide linker and RGD as the tumor targeting ligand. The precursor readily diffused into cancer cell membrane and was selectively cleaved in the PLGVRG linker by gelatinase, which is overexpressed in tumor environment. This enzymatic reaction enhanced the hydrophobicity of the molecules and reduced their steric hindrance, resulting in their self-assembly for cancer therapy.
4.3 | In situ self-assembly-based control of cellular adhesion and release, immunoregulation, and cellular regulation

In situ formation of self-assembled nanostructures was cytocompatibly induced in the presence of living cells by utilizing metal ions naturally occurring in the body (magnesium ions) and clinically used organic ligands (bisphosphonate) to regulate cellular adhesion and release and immunoregulation (Figure 5A). Notably, reversible disassembly was cytocompatibly induced by utilizing clinically used chelators (EDTA). This reversible self-assembly and disassembly enabled the remote control at prescribed time points for regulating cellular adhesion, release, mechanotransduction, and immunoregulation. In a recent study, reversible assembly and disassembly of cell-adhesive magnesium ion-presenting nanoparticles on the surface of bisphosphonate-coated AuNPs regulated reversible cell adhesion and release in vivo, respectively, and controlled cyclic cellular adhesion and patterning. In situ heterodimeric assembly of both RGD ligand- and magnesium ion-active nanomaterials further promoted focal adhesion, spreading, and osteogenic differentiation of hMSCs. Co-presentation of RGD ligands and magnesium ions was found to stimulate focal adhesion kinase and RhoA to activate ROCK, thus facilitating mechanotransduction signaling of YAP. In another study, in situ self-assembly-mediated presentation of ligand and metal ions temporally stimulated the adhesion and pro-regenerative M2 macrophages polarization via ROCK signaling in vivo while inhibiting pro-inflammatory M1 macrophage polarization. This swift and non-toxic in situ self-assembly including diverse biofunctional moieties presented a promising tool to regulate host responses to implants. In a recent study, specific living neurons were genetically instructed to guide chemical synthesis of electrically conductive polymers at the plasma membrane (Figure 5B). The synthesized chemical assembly of electroactive polymers preserved neuronal viability, remodeled membrane properties, and regulated cell type-specific behaviors in freely moving animals confirmed by electrophysiological and behavioral analyses.

4.4 | In situ self-assembly-based control of cancer therapy

In situ self-assembly has been utilized for cancer therapy typically by forming nanomaterials on the cell surface or inside the cells. For example, the metal ion-peptide-based in situ self-assembly of nanofibers from nanoparticles was harnessed for cancer therapy. Peptide-based building blocks including bispyrene motif, KLVFF motif, and RGD were found to bind to integrin of cells to form nanofibers on the surface of living cancer cells to induce their apoptosis. Furthermore, in situ self-assembly was intracellularly induced for cancer therapy applications. Cellular enzyme-triggered biochemical reactions were utilized for in situ self-assembly in the cells. This reaction occurred intracellularly to selectively inhibit drug-resistant cancer cells exhibiting high carboxylesterase activities, such as triple negative breast cancer cells and platinum-resistant ovarian cells (Figure 5C). The selectivity of this in situ self-assembly was validated for cancer cells to cause their apoptosis or necroptosis. In another study, in situ self-assembly was intracellularly induced to form nanofibers via hydrogelation. This gelation utilized matrix metalloproteinase-7, which is excessively secreted by cancer cells. The self-assembled nanofibers impaired cellular function to selectively trigger apoptosis of the cancer cells. In a recent study, taxol derivative was employed to trigger cellular furin-mediated enzymatic reaction for the self-assembly of the taxol nanoparticles, which were cleaved by esterases to release free taxol. This taxol suppressed depolymerization of tubulin to inhibit the proliferation of cancer cells and tumor progression in vivo. In addition to the intracellular self-assembly, small molecule precursor was shown to self-assemble into nanofibers via an enzymatic reaction in tumor sites in vivo. This self-assembly was triggered by gelatinase, an enzyme overexpressed in tumor environment. The self-assembled fibrous structure was utilized for photoacoustic imaging and inhibiting tumor progression in vivo.

4.5 | In situ degradation-based control of cancer therapy

Not only in situ self-assembly-based control, metal ion-based nanoprodrugs utilizing biodegradable nanomaterials can be exploited to remotely trigger in situ chemical reactions for tumor chemodynamic therapy (CDT). Degradable nanoengineered prodrugs release tumor drugs, such as reactive oxygen species (ROS) via Fenton reaction, a catalytic process in which hydrogen peroxide is converted into toxic hydroxyl free radical. Bu group synthesized transferrin-modified MgO2 nanosheets and demonstrated that these biodegradable nanoprodrugs are suitable for tumor CDT. In the acidic tumor environment, MgO2 nanosheets release both nontoxic Mg2+ and high amount of H2O2. Fe3+ released from transferrin subsequently reacted with H2O2, which produced ·OH exerting cytotoxicity to cancer cells. Similarly, amorphous iron nanoparticles in a mild acidic tumor microenvironment can undergo degradation that releases ferrous ion to generate toxic ·OH via Fenton reaction. In another
study, pH-sensitive sodium-hyaluronate-modified CaO2 nanoparticles were synthesized, which can release Ca2+ and H2O2 in cells. A disproportionate amount of cellular H2O2 and free Ca2+ overload induce tumor calcification and subsequent cell death.72

5 | ULTRASOUND-BASED CONTROL OF DYNAMIC NANOBIO MEDICAL ENGINEERING

Electrical stimulation of cells and excitable tissues, such as the nervous, bone, and muscle tissues, can be achieved invasively with the use of electrodes and wires at the diseased or damaged sites. Piezoelectric materials offer an indirect method of exerting electrical stimulation. The piezoelectric effect is a reversible process where piezoelectric materials not only can generate electrical charges as a result of an applied mechanical force but also generate a mechanical strain as a result of an applied electrical field.73 Furthermore, the piezoelectric effect can be induced with tissue-penetrative ultrasound stimuli generating electrical charges. By harnessing piezoelectric materials, mechanical stimulation is converted to electrical stimulation without implanting electrodes. This can be activated by mechanical forces, such as compression and vibration, which naturally occur in native tissues74 or can be remotely triggered by the application of ultrasound. In this review, we focus on the remote activation of piezoelectric materials by mechanical, electrical, and ultrasound stimuli for dynamic nanobiomedical engineering.

5.1 | Piezoelectric materials

Piezoelectric materials, such as biocompatible polymers and ceramics, have been utilized to dynamically interact with living cells, particularly for the remote electrical stimulation of excitable tissues.73,75 Piezoelectric materials were fabricated into flexible 3D fibrous scaffolds using poly(vinylidene fluoride-trifluoroethylene) piezoelectric polymer.76 An application of cyclic mechanical compression to these materials produced electric stimuli to regulate differentiation of hMSCs. Reverse piezoelectric effect was used to generate a mechanical vibration resulting from an applied electrical field. The nanoscale sinusoidal vibration of 10-14 nm displacement at 1 kHz frequency was generated by a piezoelectric ceramic actuator attached to culture dish.77 This generated nanoscale sinusoidal vibrations were exerted to MSCs to trigger mechanotransductive signaling, thereby mediating the differentiation of MSCs into osteoblasts. In another study, this nanoscale sinusoidal vibration was exerted to 3D biocompatible collagen materials to mediate osteogenic differentiation of MSCs.78

Piezoelectric materials composed of polymers, nanoparticles, and polymer-nanoparticle composite were developed for remote ultrasound stimulation. Polyvinylidene fluoride was employed as piezoelectric polymer simply to exert electric stimulation by converting ultrasound to electric stimuli, thereby inducing signal transduction and neuronal differentiation of cells.79 Tetragonal barium titanate nanoparticles were exploited as piezoelectric materials to enable the conversion of ultrasound to electrical stimuli within cells.80 The piezoelectric nanoparticle-loaded cells were shown to remotely stimulate ion influxes to induce neuronal differentiation of cells in response to ultrasonic stimuli. The micromachines were designed as composites composed of piezoelectric polymer materials in which MNPs were dispersed.81 Piezoelectric polymer functioned as an ultrasound-responsive electrostimulation platform for cells, whereas the MNPs enabled the magnetic actuation of the micromachines. By applying a rotating magnetic field, the micromachines exhibit the active motion. Under an application of ultrasound, the micromachines are electrically polarized to induce neuronal differentiation of cells loaded on their surface.

5.2 | Mechanical, electrical, and ultrasound-based control of cellular signaling, delivery, and differentiation

Harnessing piezoelectric materials allows active control of electrical or mechanical stimulation to the materials, thereby dynamically facilitating cellular signaling, delivery, and differentiation through mechanical, electrical, and ultrasound stimuli. Among such stimuli, remotely activatable tissue-penetrative ultrasound is a promising candidate for noninvasive clinical therapies. Flexible 3D fibrous scaffolds using piezoelectric polymer generated electric output in response to cyclic mechanical stimulation to regulate differentiation of hMSCs.76 Piezoelectric materials that exhibited low-voltage output promoted chondrogenic differentiation, whereas piezoelectric materials exhibiting high-voltage output promoted osteogenic differentiation, which highlights the potential of utilizing these materials for tissue engineering. Reverse piezoelectric effect was utilized to exert nanoscale vibration to culture dish connected to the piezoelectric ceramic actuator.77 This mechanical stimulation to MSCs triggered their RhoA-mediated adhesion and osteogenic differentiation. In another study, this nanoscale sinusoidal vibration exerted to 3D collagen materials facilitated the adhesion and cytoskeletal tension development in MSCs to induce their osteogenic differentiation.78 This stem cell differenti-
ation was achieved through the activation of β-catenin signaling in the absence of osteoinductive chemicals and/or growth factors.

Instead of mechanical and electrical stimulation, remotely activatable tissue-penetrative ultrasound stimuli was harnessed for piezoelectric materials that convert ultrasound to electric stimulation primarily for facilitating neuronal differentiation of cells. For instance, polyvinylidene fluoride was utilized to generate electrical charges on the surface of materials via ultrasound stimulation to activate calcium channels, thereby inducing the generation of neurites via cyclic adenosine monophosphate-dependent signaling pathway. The piezoelectric nanoparticle-loaded cells were shown to induce calcium and sodium fluxes and activate voltage-gated membrane channels to mediate the neurite outgrowth and neural differentiation. The MNP-embedded piezoelectric micromachines were shown to simultaneously enable the magnetic actuation of the micromachines and ultrasound-responsive electrostimulation of the cells loaded on their surface. This approach is promising for targeted cell transportation and differentiation in vivo. The combinational use of ultrasound with piezoelectric materials offers promising potential for the development of noninvasive neuroregenerative devices.

6 | OUTLOOK AND CHALLENGES

The remote and active control of ECM-mimicking nanoengineered materials can regulate and unravel complex cell-material interactions, thus benefiting the advancement of convenient, nontoxic, site-specific, and on-demand patient-tailorable therapies. Continuous advancement of these materials will uniquely help understand how dynamic changes occur in the interactions between host cells and the native nanostructured ECM at the molecular level, which arise at disease and trauma sites either locally or systemically. Despite these tremendous benefits, the development of the remotely and actively controllable materials currently lies in the proof-of-concept stage. Various remote and active stimuli present distinct opportunities and challenges, which necessitate the choice of optimal stimulus to address particular so far unmet clinical challenges or unresolved fundamental questions.

Each stimulus and responsive material need to be chosen for their specific clinical use to ensure their safe and effective application. Magnetic field and ultrasound approaches appear to exhibit superior tissue-penetrative capability and can thus be applied for deep interior tissues. High-intensity magnetic field and ultrasound approaches have been noninvasively and safely applied in MR and ultrasound imaging of patients, respectively. Because UV and visible light are readily absorbed by living tissues, light-controllable materials responding to such wavelengths are limited to noninvasive applications in shallow exterior tissues, such as skin and subcutaneous tissues. NIR light can penetrate to deep tissues with less absorption of light and thus the use of the NIR-responsive UCNPs is desirable for deep interior tissues. In situ self-assembly necessitates a minimally invasive injection of cytocompatible ligands, precursors, peptides, and ions, which may require precise control in reaching deep interior tissues. The application of mechanical, electrical, and ultrasound stimuli with piezoelectric materials is beneficial in activating electrically excitable tissues, such as the nervous, bone, and muscle tissues. Among these stimuli used for piezoelectric materials, tissue-penetrative ultrasound stimulus is preferable for noninvasive application to deep anatomical tissues.

Clinical translation of these materials necessitates their convenient and economic use for patients and clinicians. In this perspective, among such remote and active stimuli, in situ self-assembly offers simple controllability and cost-effectiveness via an injection of cyto compatible ligands, precursors, peptides, and ions into the targeted sites without the need for external devices to generate physical stimulation via magnetic fields, light, mechanical movement, electricity, and ultrasound. It is also critical to design these materials to respond to the short-time application of a stimulus for their convenient use toward clinical therapies. For the widespread use of these materials, their controllable and reproducible responses to various stimuli need to be precisely optimized. For example, synchronization of the motion of superparamagnetic nanoparticles in response to an applied strength of the magnetic field needs to be controlled. UCNPs need to be precisely designed to exhibit high light conversion efficiency for their effective control. Nonetheless, NIR light can be applied with high spatial precision, thus ensuring spatial controllability. In situ self-assembly needs to be targeted for specific sites to minimize potential dilution of injected solution with body fluids in vivo.

For the long-term application of these materials (particularly the use of nanomaterials), their long-term stability and local and systemic nontoxicity need to be ensured. Iron oxide MNPs may be safer than lanthanide-doped UCNPs. In situ self-assembly utilizes cyto compatible monomers and ions. The self-assembled nanoparticles typically degrade and thus may not be stable over the long term, which may be beneficial for certain applications, such as sustained drug delivery. Indeed, the in situ self-assembly can be repeatedly induced to realize its long-term use via multiple injections of cyto-compatible ligands, precursors, peptides, and ions. Because native tissues are developed over a long period, these materials
need to be designed to maintain their effectiveness albeit with newly formed native tissues in proximity to these materials.

Remotely and actively controllable nanoengineered materials present unique opportunities to manipulate and understand dynamic nanoscale interactions between cells and bioactive nanostructured materials, which regulate diverse cellular processes, such as cellular signal transduction, adhesion, detachment, mechanotransduction, differentiation, polarization, and apoptosis. Although they are useful for the remote control of regenerative therapy, immunoengineering, drug delivery, cancer therapy, and biocatalysis, dynamic cell-regulatory mechanisms at the molecular level can be fundamentally unraveled with the use of these unique materials, which cannot be achieved with static and macroscale materials. Further development of these materials will facilitate our understanding of signaling cascades from the cell membrane to the nucleus and provide the means to target specific signaling molecules at prescribed time points. In addition, these remotely and actively controllable nanoengineered materials emulate specific dynamic and complex attributes of the ECM. Further advancement of these materials is desired to reflect the 3D complexity of cell-ECM interactions by the assembly of nanomaterials for enabling 3D cell-, tissue-, and organ-level control. In addition to dimensional complexity, these materials can be advanced to exhibit reversibility, respond to dual stimuli to perform sophisticated functions, and enable MR, photoluminescence, and ultrasound imaging.

Remotely and actively controllable nanoengineered materials with the choice of optimal stimulus can address unmet clinical challenges or unresolved fundamental questions, thus opening up new avenues for simple, safe, site-specific, and on-demand therapies tailored for specific disease conditions of patients. Except for the in situ self-assembly, the necessity of external devices to generate physical stimuli, such as magnetic field, light, and ultrasound, for the control of these materials may potentially require the development of portable devices for their convenient use for patients and clinicians. It is of paramount importance to continue to advance the design of these materials to mimic dynamic and nanoscale 3D complexity of cell-ECM interactions with multiresponsiveness, reversibility, cost-effectiveness, reproducibility, long-term stability, and local and systemic nontoxicity. The advancement of these materials will offer unprecedented and convenient modalities in clinical therapies to benefit clinical practices in healthcare systems.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

ACKNOWLEDGMENTS
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2020R1C1C1011038). This work was also supported by a Korea University Grant.

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How to cite this article: Kim Y, Choi H, Shin JE, Bae G, Thangam R, Kang H. Remote active control of nanoengineered materials for dynamic nanobiomedical engineering. VIEW. 2020:1: 20200029. https://doi.org/10.1002/VIW.20200029