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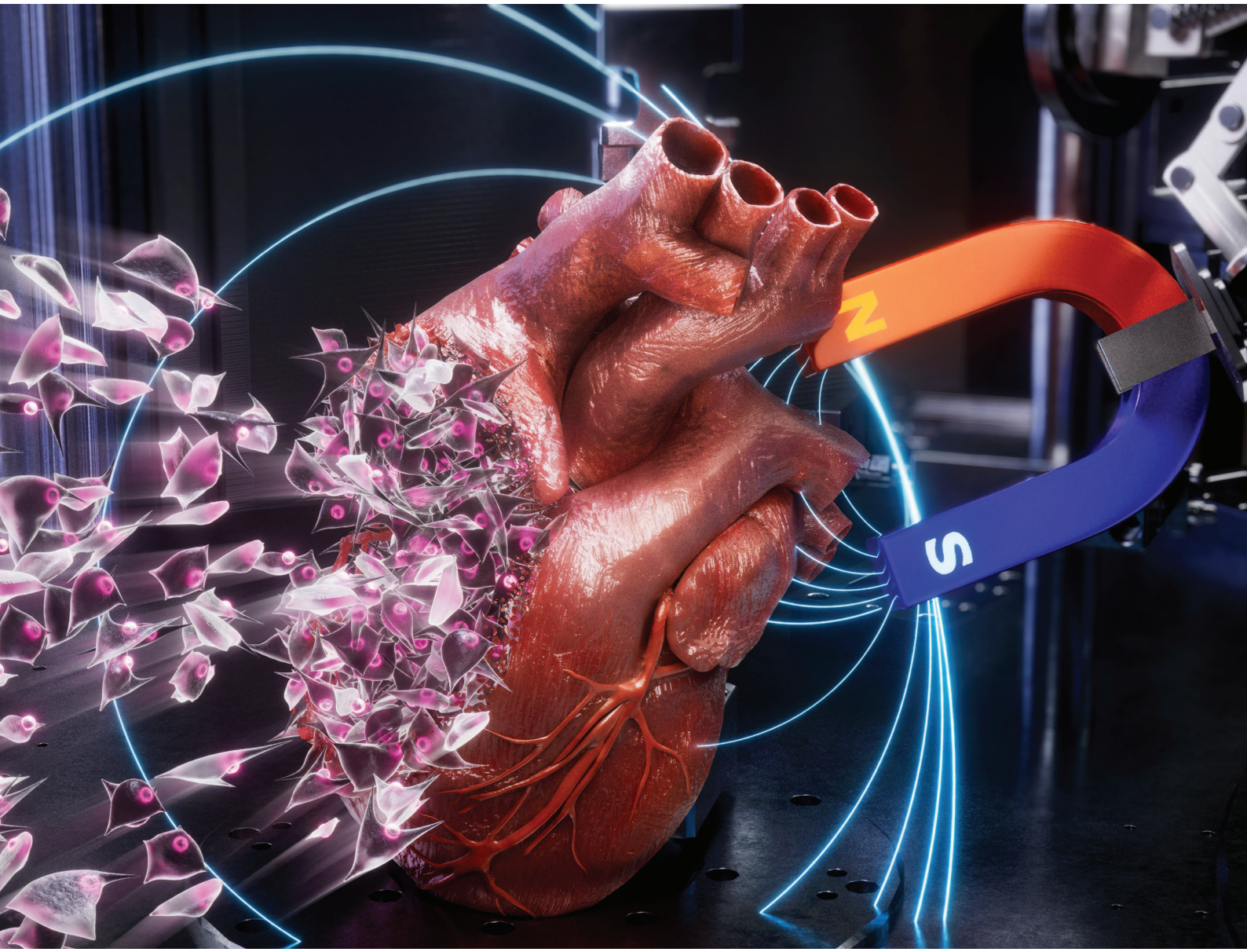

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REVIEW ARTICLE

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Magnetic-based tissue engineering: principles, applications, and future prospects in biofabrication

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Magnetic-based tissue engineering: principles, applications, and future prospects in biofabrication

Hwanyong Choi [a] and Jinah Jang *[a,b,c,d,e]

Magnetic-based tissue engineering (MagTE) is a rapidly advancing interdisciplinary field that integrates magnetic materials and external magnetic fields with tissue engineering principles to manipulate cells, biomaterials, and biological environments for developing functional tissue substitutes. This review provides a comprehensive overview of MagTE, covering its fundamentals, applications, and future directions within the biofabrication domain. The magnetic properties of paramagnetic, ferromagnetic, ferrimagnetic, and superparamagnetic materials are discussed, along with mechanisms of magnetic actuation through forces and torques. MagTE applications are categorized into cell manipulation and stimulation. Direct and indirect manipulation techniques also enable precise control of cell alignment, patterning, and assembly into complex three-dimensional structures, such as cell sheets, spheroids, and organoids. Stimulation approaches—mechanical, thermal, electrical, and biochemical—exploit interactions between magnetic particles and external fields to elicit specific physiological responses and support tissue regeneration. We then conclude by addressing the current limitations of MagTE and proposing strategies to overcome these challenges.

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1. Introduction

Tissue engineering is an interdisciplinary field that integrates biomaterials, cells, and biochemical and physicochemical factors to develop biological substitutes capable of restoring, maintaining, or enhancing damaged tissues or organs.[1] This field has demonstrated significant potential in addressing key challenges associated with existing medical technologies, such as organ donor shortages and immune rejection while accelerating tissue regeneration.[2] Recent efforts in tissue engineering have focused on replicating the intricate three-dimensional (3D) structures and functions of the *in vivo* microenvironment by systematically delivering complex physical and chemical signals.[3,4]

A notable direction within this evolving field is biofabrication, a subfield encompassing processes for artificially producing living tissues using cells and biomaterials as building blocks. Leveraging cutting-edge technologies, biofabrication achieves precision in tissue organization, cellular alignment, and functional integration.[5–8] For example, the production of cellular aggregates (*e.g.*, spheroids and organoids) utilizes self-assembling multicellular aggregates to mimic the 3D architecture and functionality of native tissues.[9,10] At the same time, cell sheet methods create layered cell structures without scaffolds to facilitate integration with host tissues.[11,12] In addition, bioprinting technology employs layer-by-layer deposition of bioinks—comprising cells, biomaterials, and growth factors—to construct complex tissue architectures with spatial control.[2,13–19] Innovations such as cell-laden hydrogel systems[20–22] and microfluidics[23–26] enable dynamic simulations of tissue environments, facilitate vascularization, and address critical challenges like replicating the extracellular matrix (ECM), improving mechanical stability, and achieving functional complexity.

These advancements support customized tissue design, complex organ simulation, and automated mass production, expanding applications in regenerative medicine and the pharmaceutical industry.[19,27] In regenerative medicine, biofabrication enables the design of custom implants tailored to individual patients, while in the pharmaceutical sector, biofab-

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ricated tissue models facilitate high-throughput drug screening, reduce reliance on animal testing, and enhance drug development and toxicology assessments.[28,29] Moreover, biofabrication allows for disease modeling by recreating pathological conditions *in vitro* to study disease progression and therapeutic responses.[30] Ultimately, the field aspires to create fully functional, transplantable organs, addressing organ shortages and revolutionizing organ replacement therapies.[31] By integrating biological, mechanical, and chemical cues to guide cell behavior, promote tissue maturation, and mimic *in vivo* conditions—including gradients of oxygen, nutrients, and mechanical forces—biofabrication enables more realistic and effective tissue models.

Despite its progress, biofabrication faces challenges in replicating the functional complexity of *in vivo* tissues and organs.[27,32,33] Current research focuses on refining fine structural details, optimizing intercellular signal transmission, and incorporating diverse cell types into tissue-specific microenvironments. Advanced vascularization strategies are being explored to ensure oxygen and nutrient supply, minimizing cell necrosis during scale-up.[34–37] Additionally, advancements in equipment and materials aim to enable dynamic modulation of *in vivo*-like conditions after fabrication, including applying mechanical and chemical stimuli and inducing structural deformations.[38,39] These capabilities are critical for simulating dynamic changes in clinical settings, such as post-implant remodeling and patient-specific stimulation protocols.

One emerging approach to address these limitations is magnetic-based tissue engineering (MagTE), which integrates magnetic materials and external magnetic fields to manipulate cells, biomaterials, and tissue environments. MagTE employs magnetic particles incorporated into cells or scaffolds, enabling remote interactions under an external magnetic field.[40] For instance, magnetic-labeled cells, created by encapsulating magnetic particles within cells, can be precisely positioned and aligned using external fields. This simplifies the formation of 3D structures like spheroids and organoids while increasing efficiency.[41–43] Magnetic particles also respond to external magnetic fields by generating forces, torques, vibrations, or oscillations, enabling non-invasive stimulation—including mechanical, thermal, and electrical stimuli—within tissues.[44] These features allow for precise control over cell movement, alignment, drug delivery, and tissue formation, offering possibilities for patient-specific stimulation and post-implant remodeling. As such, MagTE is emerging as a transformative technology in next-generation tissue engineering.

This paper systematically examines the potential of MagTE in biofabrication. The fundamental principles of magnetic particles and magnetic fields are primarily summarized, followed by a review of current cell- and tissue-level applications. Beyond summarizing the fundamental mechanisms of magnetic actuation, this paper emphasizes the integration of MagTE into broader biofabrication workflows, exploring its roles not only in cellular and tissue assembly but also in functional maturation and clinical translation. In addition, the paper explores potential expansions of MagTE into areas such as magnetic field-based robotics, which have yet to be fully integrated into biofabrication. Finally, future directions and strategies for clinical applications of MagTE in the biofabrication field are discussed (Fig. 1).

2. Fundamentals of magnetic-based tissue engineering

MagTE employs external magnetic fields to perform various functions essential for tissue engineering. To fully utilize MagTE, it is crucial to understand the selection and characteristics of magnetic particles, their manufacturing methods, and the properties of magnetic fields. The physical and chemical properties of magnetic particles, such as biocompatibility, remanence, and saturation magnetization, are influenced by factors such as particle size and material composition. Additionally, the applied magnetic field—whether static or dynamic—generates different operational mechanisms, including force and torque. This section will first introduce the types of magnetic particle, the methods used to implement magnetic fields and the effects these fields have on the actuation of magnetic particles.

2.1. Magnetic properties of magnetic materials

To classify and understand magnetic materials, it is essential to examine several key parameters related to a material's magnetization, including magnetic susceptibility (χ_m), remanence (M_r), and coercivity (H_c). These parameters determine how a material responds to an external magnetic field and the magnetization state it retains once the field is removed.[45]

2.1.1. Key parameters of magnetic materials. Understanding how magnetic materials interact with external magnetic fields and how they retain their magnetization requires an understanding of parameters such as magnetization (M), χ_m, M_r, and H_c. Magnetization (M) refers to the extent to which the magnetic moments of atoms or molecules within a material align in a specific direction. It varies with the strength of the external magnetic field (H). A higher magnetization value indicates that the material is strongly magnetized and behaves actively as a magnet.

Magnetic susceptibility (χ_m) quantifies how easily a material becomes magnetized when exposed to an external magnetic field. It is defined as the rate of change in magnetization with respect to the magnetic field, expressed as $\chi_m = \partial M/\partial H$. A higher susceptibility means the material exhibits significant magnetization even under a weak magnetic field. Magnetic susceptibility can be either positive (+) or negative (−), and its magnitude indicates the material's magnetization characteristics.

Generally, its magnetization increases until it reaches a point of saturation as a material is exposed to an external magnetic field. Beyond this point, further increases in the magnetic field do not result in greater magnetization. When the magnetic field is removed, the remaining magnetization is

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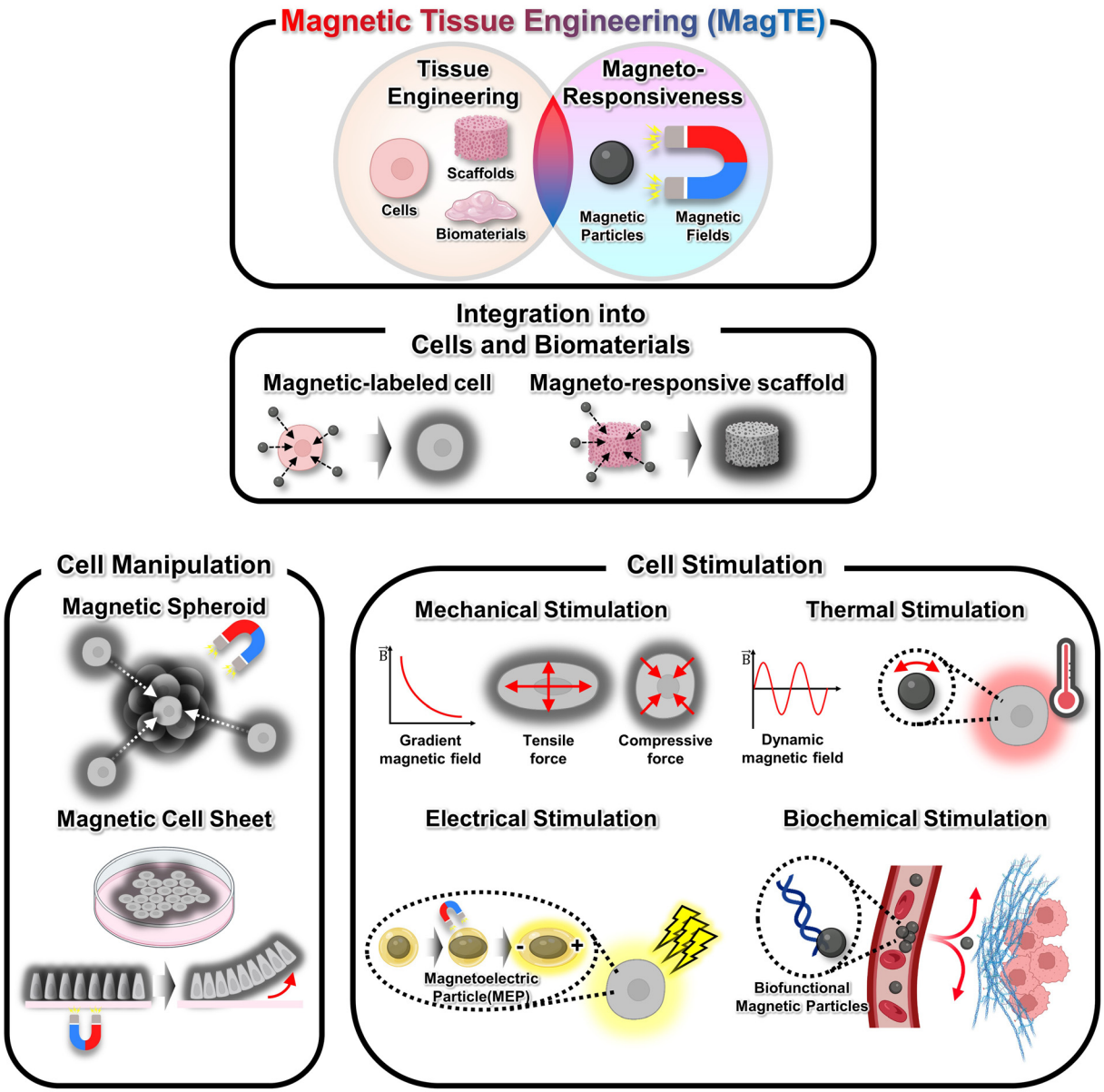

Fig. 1 Illustration of an overview of this review: the fundamental principles and applications of magnetic-based tissue engineering.

termed remanence (M_r). Materials with high remanence maintain strong magnetization even without an external magnetic field. Coercivity (H_c) is the strength of the reverse magnetic field required to remove the remanence. Materials with high coercivity are difficult to demagnetize, exhibiting permanent magnet-like properties, whereas those with low coercivity easily return to their initial state after the field is removed. These parameters provide crucial information about the magnetic behavior of materials and are essential for selecting the appropriate materials for specific applications.

2.1.2. Classification of magnetic materials. Magnetic materials used in MagTE can be broadly classified into four categories: paramagnetic, ferromagnetic, ferrimagnetic, and superparamagnetic.[46–48]

Paramagnetic materials have magnetic moments that are randomly aligned in the absence of an external magnetic field, resulting in a net magnetization close to zero. When an external magnetic field is applied, the magnetic moments slightly align, producing a weak net magnetization. However, once the magnetic field is removed, the magnetization disappears due to thermal fluctuations. Although these materials exhibit positive magnetic susceptibility, their susceptibility is very small ($\chi_m \ll 1$), limiting their functionality as strong magnets. Examples include aluminum (Al), titanium (Ti), and tungsten (W) (Fig. 2A).[46] Ferromagnetic materials contain magnetic domains, within which all atomic or molecular magnetic moments are aligned in the same direction, exhibiting spontaneous magnetization even without an external magnetic

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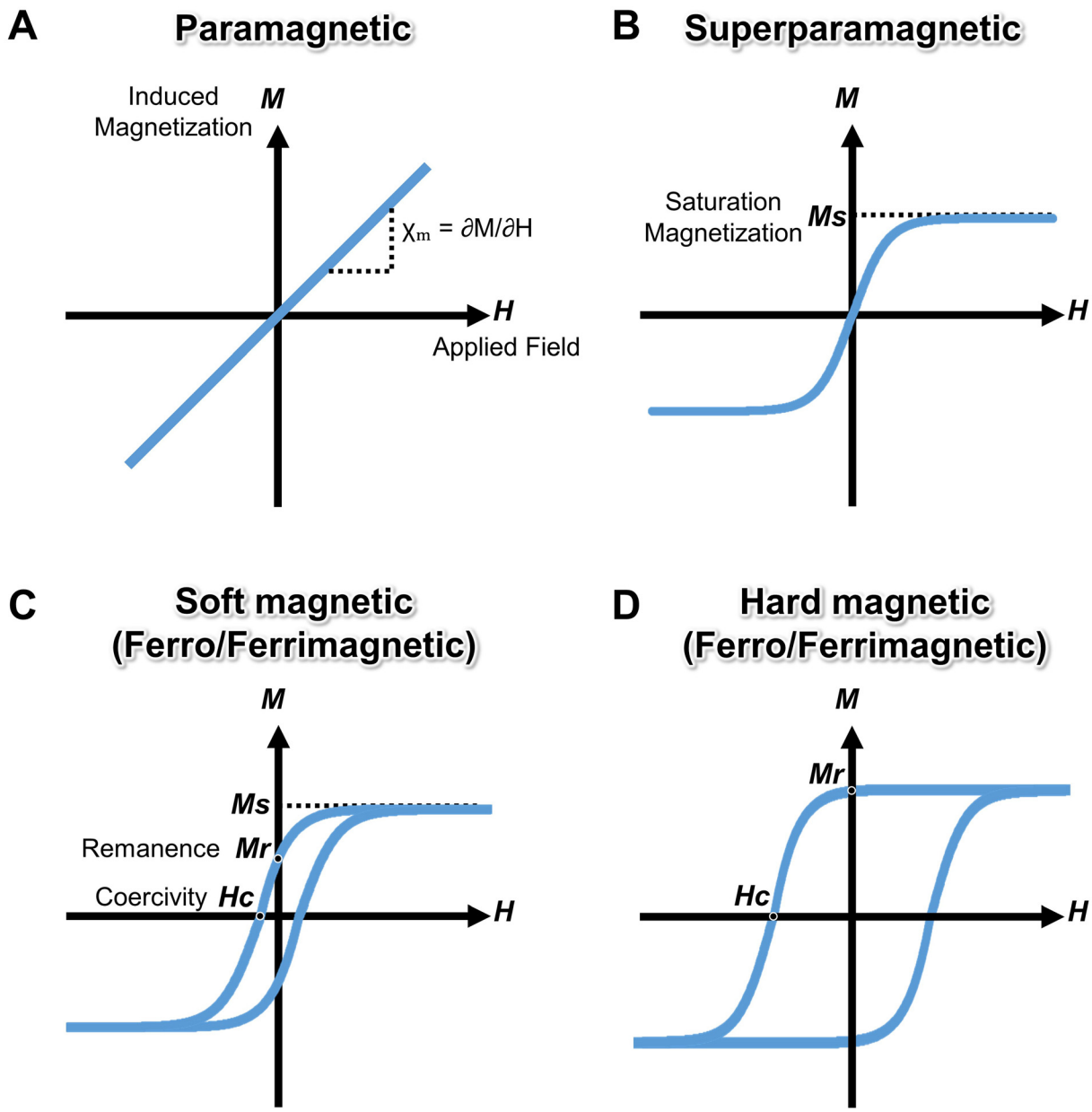

Fig. 2 Magnetization behaviors of different types of magnetic material. (A) Paramagnetic materials exhibit a linear relationship between the magnetization and applied magnetic field, with no hysteresis. (B) Superparamagnetic materials show an S-shaped curve without remanence or coercivity, indicating no residual magnetization once the field is removed. (C) Soft magnetic materials (ferromagnetic/ferrimagnetic) display a narrow hysteresis loop, meaning they can be easily magnetized and demagnetized. (D) Hard magnetic materials (ferromagnetic/ferrimagnetic) exhibit a wide hysteresis loop, retaining significant magnetization even after the external field is removed.

field. Applying an external magnetic field aligns all domains, achieving a saturated state. When the external magnetic field is removed, some domains remain aligned, resulting in significant remanence. These materials typically exhibit high magnetic susceptibility ($\chi_m \gg 1$). Examples include iron (Fe), nickel (Ni), cobalt (Co), and their alloys, which are commonly used as magnets due to their high remanence.[46]

Ferrimagnetic materials are similar to ferromagnetic materials in that they exhibit spontaneous magnetization. However, in these materials, some magnetic moments within the domains are aligned in opposite directions (antiparallel), although their magnitudes do not completely cancel out. This results in a non-zero net magnetization. Ferrimagnetic materials exhibit a more complex structure than ferromagnetic materials. Specifically, the spins of two groups (A and B) are aligned in opposite directions. However, the magnetic moments of these groups differ in magnitude, resulting in one side dominating and retaining strong magnetization even after the external magnetic field is removed. Ferrimagnetic materials exhibit high magnetic susceptibility and remanence,

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similar to ferromagnetic materials, but are structurally more complex. Representative examples include magnetite (Fe_3O_4) and maghemite (γ-Fe_2O_3) (Fig. 2C).[46]

Soft magnetic materials are a subset of ferromagnetic and ferrimagnetic materials with low coercivity and low remanence. These materials are easily magnetized and demagnetized, responding quickly to magnetic fields. However, they are not suitable as permanent magnets, as their remanence diminishes after the magnetic field is removed. Soft magnetic materials are primarily used in electromagnetic devices, such as transformer cores and motors, due to their low energy loss in alternating magnetic fields (AMF). Examples include carbonyl iron and silicon steel (Fig. 2C).[47]

Hard magnetic materials, on the other hand, have high coercivity and high remanence, allowing them to maintain strong magnetization even after the external magnetic field is removed. These materials can act as miniature permanent magnets, making them suitable for applications requiring torque-based deformations, such as rotation or bending in uniform magnetic fields. Examples include NdFeB, SmCo, and ferrites (*e.g.*, $BaFe_{12}O_{19}$) (Fig. 2D).[47]

Superparamagnetic materials are typically ferromagnetic or ferrimagnetic materials that exhibit superparamagnetic behavior when the size of individual particles becomes much smaller than the magnetic domain size, on the nanometer scale. In these materials, thermal fluctuations can eliminate remanence when the external magnetic field is removed, causing their magnetization to rapidly randomize. Despite exhibiting high magnetization in the presence of a magnetic field, superparamagnetic materials lose their remanence once the field is removed. This behavior minimizes the risk of aggregation and potential side effects on surrounding tissues, making superparamagnetic materials ideal for biological and medical applications. Common examples include iron oxide nanoparticles (such as magnetite Fe_3O_4 and maghemite γ-Fe_2O_3) and gadolinium nanoparticles (Gd_2O_3) (Fig. 2B).[48]

Although magnetic classification explains their physical behavior, the decisive factor for clinical adoption is how each material interacts with living tissues. From a biomedical standpoint, superparamagnetic materials are regarded as comparatively safe because their magnetization disappears immediately after the external field is withdrawn, eliminating any residual magnetic force; clinically approved superparamagnetic iron-oxide nanoparticles (SPIONs) exemplify this benefit. Paramagnetic materials likewise lose magnetization once the field is removed, but their biocompatibility depends largely on chemical composition—gadolinium-based compounds, for example, can accumulate in tissues and raise toxicity concerns. Ferrimagnetic materials retain partial remanent magnetization, so long-term tissue residence and chronic cellular stimulation are possible; however, when these particles are downsized to the nanoscale, the associated risks are greatly reduced. Ferromagnetic materials present the greatest safety challenge: their strong remanence can impose mechanical stress on nearby cells, and corrosion or oxidation may release metal ions such as Fe^{3+}, Co^{2+}, or Ni^{2+} into the biological milieu.[49]

To suppress the potential cytotoxicity of magnetic particles, engineers routinely employ surface-coating strategies that physically isolate the metallic core from its environment. Biocompatible, inert layers of polyethylene glycol (PEG), poly (lactic-*co*-glycolic acid) (PLGA), dextran, or silica form an effective barrier, mitigating ion leaching, oxidative stress, and inflammatory responses.[50] Further surface functionalization with targeting ligands or stealth coatings enhances colloidal stability, prolongs systemic circulation, and reduces nonspecific cellular uptake.[51] Through these approaches, the safety of magnetic particles can be secured, thereby expanding their applicability in biomedical fields.

2.2. Principles of magnetic actuation

The actuation of magnetic particles is determined by the types of particle used and the form and characteristics of the external magnetic field applied to them. Magnetic actuation fundamentally relies on the interaction between the magnetic particles and the external magnetic field, inducing physical changes primarily through magnetic force and magnetic torque. The intensity of these effects is influenced by both the physical properties of the magnetic particles and the specific form of the external magnetic field, which collectively govern the macroscopic behavior of the materials and the resulting mode of operation.[45]

2.2.1. Mechanisms of magnetic actuation. Magnetic force (F) arises when magnetic particles are exposed to an inhomogeneous magnetic field (*i.e.*, a gradient magnetic field). This force can be mathematically expressed as:

$$F = \nabla(m \cdot \mathbf{B}), \tag{1}$$

where m is the magnetic moment of the particle and $\mathbf{B}$ is the magnetic field vector. The magnetic force results from the interaction between the magnetic moment of the particle (induced by the external magnetic field) and the gradient of the field (eqn (1)). By utilizing a precisely designed inhomogeneous magnetic field, magnetic forces can be applied to move or position particles in specific directions, or to focus them in targeted areas (Fig. 3A).[45]

Magnetic torque (τ), in contrast, occurs under a uniform magnetic field and refers to the rotational force that causes the particle's magnetic moment to align with the field. This torque is expressed as:

$$\tau = m \times \mathbf{B} \tag{2}$$

Magnetic torque induces rotational motion in particles, playing a crucial role in determining their orientation (eqn (2)). By adjusting the magnetic field accordingly, particles can be made to perform rotational or vibrational movements, which can then provide mechanical stimulation to cells or scaffolds, or generate heat for thermal effects. Together, the combination of magnetic forces and torques allows for the execution of a variety of tissue engineering functions depend-

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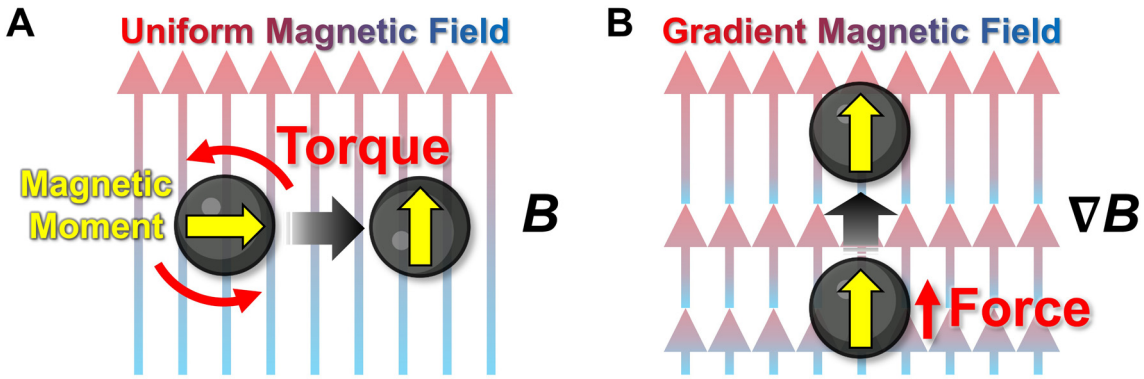

Fig. 3 Principles of magnetic actuation. (A) In a uniform magnetic field, a magnetic particle with a magnetic moment experiences torque, aligning itself with the field direction but without translational motion. (B) In a gradient magnetic field, the particle experiences force, causing it to move in the direction of increasing field strength.

ing on the specific characteristics of the magnetic particles and the external magnetic field (Fig. 3B).[45]

2.2.2. Methods of magnetic actuation. Magnetic fields can be generated either by permanent magnets or by electric currents through electromagnetic induction. Electromagnetic induction refers to the phenomenon where a time-varying magnetic field induces an electric field, and conversely, an electric current generates a magnetic field. The relationship between these magnetic and electric fields is expressed as follows:

$$\nabla \times E = -\frac{\partial B}{\partial t} \quad (3)$$

Here, E denotes the induced electric field and B represents the magnetic flux density. This relationship, also known as Faraday's law, explains that when a magnetic field changes over time, an electric field is induced along a closed loop, thereby generating an electric current. Conversely, by controlling the magnitude and direction of the electric current, the strength and orientation of the magnetic field generated in a given space can be precisely modulated (eqn (3)).[52] Magnetic fields are classified based on their characteristics into static and dynamic fields, as well as uniform and gradient fields. This classification is essential for selecting the appropriate magnetic field for specific applications.[45] Static magnetic fields are generated using permanent magnets or direct current (DC) coils and maintain a constant strength and direction. Dynamic magnetic fields, in contrast, are generated using alternating current (AC) or electromagnetic induction, and their strength and direction vary over time. Dynamic magnetic fields can take forms such as alternating magnetic fields (AMF), rotating magnetic fields, and pulsed magnetic fields. These fields can induce repetitive movements or vibrations in magnetic particles, generating heat (hyperthermia) or applying mechanical stimulation to cells. Gradient magnetic fields are characterized by spatial variations in the magnetic field's strength and direction. These fields cause magnetic particles to experience forces that move or focus on them in specific directions. Gradient magnetic fields can easily be generated using permanent magnets or electromagnets arranged with a single pole, and are useful for adjusting the positioning or arrangement of particles. Uniform magnetic fields maintain consistent strength and direction across a specific area, typically generated using devices like Helmholtz coils. These fields are primarily used to induce rotational or bending movements in magnetic particles.

2.2.3. Reactions of magnetic particles to various magnetic fields. The response of magnetic particles to external magnetic fields varies depending on the type of material (*e.g.*, paramagnetic, ferromagnetic, superparamagnetic) and the characteristics of the applied magnetic fields. Understanding these interactions is crucial for effectively adjusting magnetic systems to achieve the desired outcomes. Paramagnetic materials exhibit weak magnetization in the presence of an external magnetic field but lose all magnetization once the field is removed. These materials primarily respond to weak magnetic forces under gradient magnetic fields, causing them to move or focus in specific directions. However, due to their limited response, paramagnetic materials have fewer applications in MagTE compared with other materials.[46] Ferromagnetic and ferrimagnetic materials, particularly hard magnetic materials, exhibit high magnetic susceptibility and significant remanence. Once magnetized, these materials retain their magnetization even after the external magnetic field is removed. When a magnetic field is applied, ferromagnetic materials experience both magnetic forces and torques, which induce complex deformations such as bending, twisting, contraction, and extension. These behaviors enable precise 3D movements in soft robots and other applications. Soft magnetic materials, in contrast, can be easily magnetized and demagnetized, making them ideal for dynamic applications such as transformers and magnetic actuators.[46] Superparamagnetic materials exhibit high magnetization in an external magnetic field due to their high magnetic susceptibility but quickly lose their magnetization once the field is removed. This property makes superparamagnetic particles

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particularly useful in applications such as magnetic hyperthermia, where particles are vibrated under dynamic magnetic fields to generate heat or in temperature-triggered drug release systems. Under gradient magnetic fields, superparamagnetic particles experience strong forces that enable the precise movement or arrangement of cells or molecules in microenvironments. Unlike other materials, superparamagnetic particles do not experience substantial magnetization in uniform magnetic fields, meaning their primary mechanism of action is based on force-induced movement rather than torque-based rotational movements.[46] By strategically combining interactions between magnetic fields and particle behaviors, MagTE can successfully implement various functions such as cell and tissue alignment, scaffold deformation, and cellular stimulation.

2.3. Magnetic particle sizes and their properties

Magnetic particles in MagTE enhance tissue engineering by leveraging magnetic fields at both cellular and tissue levels. Their size influences their properties and integration into cells or biomaterials, making it essential to summarize how particles of different sizes interact with cells and biomaterials and affect their functions.

Magnetic nanoparticles (MNPs, 1–100 nm) possess a high surface area-to-volume ratio that facilitates efficient cellular uptake *via* endocytosis, enabling magnetic cellular labeling. Surface functionalization—with coatings such as carboxyl (–COOH), amino ($-NH_2$), silanes, or polymers (*e.g.*, PEG)—allows these nanoparticles to bind to proteins, peptides, antibodies, DNA, RNA, or signaling ligands. Thanks to these versatile properties, magnetically labeled cells are widely used for applications like cell tracking, magnetic field-guided cell manipulation, and drug delivery. Additionally, MNPs typically exhibit superparamagnetic behavior, meaning their magnetization vanishes when the external magnetic field is removed, which minimizes aggregation and enhances biocompatibility and safety. Their high magnetic moments and stability make them invaluable for tissue engineering and cell-based therapies.

Magnetic microparticles (MMPs, 1–100 μm) are significantly larger than MNPs and typically exhibit ferromagnetic or ferrimagnetic properties with stronger magnetization. Easily surface-modified for cell attachment through adsorption or covalent bonding, these particles enable magnetic cellular labeling[53,54] and generate substantial forces and torques under external magnetic fields, allowing for the precise manipulation of cells into patterned structures. Moreover, MMPs can be incorporated into hydrogels or polymer scaffolds to enhance mechanical properties and promote cell attachment, with magnetic fields used to dynamically reshape scaffolds or control cell positioning. These features make MMPs indispensable for forming complex 3D tissue structures and creating dynamic environments conducive to biofabrication.

Magnetic particles—from nanoparticles to microparticles—integrate with cells and biomaterials in diverse ways, facilitating cell labeling, tissue structuring, scaffold enhancement, and precise cell manipulation. Moreover, the size of magnetic particles profoundly affects their *in vivo* behavior, including biodistribution, clearance, and long-term safety. MNPs typically exhibit enhanced permeability and retention effects, allowing them to accumulate in certain tissues, particularly tumors and inflamed regions. They are primarily cleared through renal excretion if their hydrodynamic diameter is below 5 nm, or *via* hepatobiliary routes for larger nanoparticles.[55] However, as particle size increases, the management of *in vivo* degradation and clearance becomes increasingly challenging. Larger particles tend to exhibit slower or unpredictable degradation rates and prolonged tissue retention, complicating biocompatibility management.[56] Consequently, for microscale or larger magnetic particles, direct *in vivo* injection is generally avoided. Instead, current applications primarily focus on their incorporation into biomaterial scaffolds, *ex vivo* cell manipulation prior to implantation, or external magnetic field-assisted assembly processes, thereby minimizing the need for systemic distribution and enhancing localized control. To successfully leverage magnetic particles in MagTE, it is crucial to carefully consider size-dependent properties—including magnetic behavior, biodegradation, clearance, and interaction with biological systems—during material selection and application design.

3. Magnetic-based tissue engineering

MagTE leverages the unique properties of magnetic particles, which respond to external magnetic fields, for diverse applications in tissue engineering. By incorporating magnetic particles into cells or biomaterials, these components can interact remotely with external magnetic fields. MagTE technologies, particularly in the field of biofabrication, can be broadly classified into two categories based on their primary functions: cell manipulation and cell stimulation.

This section explores the development of MagTE technologies for specific purposes and methods and their subsequent applications.

3.1. Magnetic cell manipulation

A central application of MagTE is the precise control and assembly of magnetic cells. By fusing magnetic particles with cells or mixing them into cell culture media, magnetically labeled cells are created that can be non-invasively and remotely directed using magnetic fields. These fields, operating without physical contact, enable both direct and indirect cell manipulation—methods that allow cells to be aligned and patterned into desired configurations. As a result, tissue assembly processes are significantly advanced, facilitating the efficient fabrication of complex structures such as cell sheets, 3D spheroids, and organoids. These cell manipulation techniques are broadly categorized into two approaches: direct manipulation and indirect manipulation.

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3.1.1. Direct manipulation. Direct manipulation involves magnetizing cells through magnetic cellular labeling, enabling their precise positioning and assembly using external magnetic fields. This method has been applied to create artificial tissues and organ-on-chip systems by arranging magnetic-labeled cells into desired patterns. The non-contact nature of magnetic fields minimizes physical damage to cells, making this technique particularly effective for fabricating complex 3D tissue structures. Richard *et al.* demonstrated the use of magnetic cellular labeling to align cardiomyocytes in 3D, a critical step for replicating the functional characteristics of myocardial tissue (Fig. 4A-a).[57] Maghemite nanoparticles were endocytosed into cardiomyocytes for labeling, and external magnetic fields were applied to align the cells into 3D chains, imparting directionality. Following gelation, the aligned cells maintained their orientation even after removing the magnetic field (Fig. 4A-b). The resulting cell chains exhibited coordinated beating, reflecting the anisotropic structure of heart

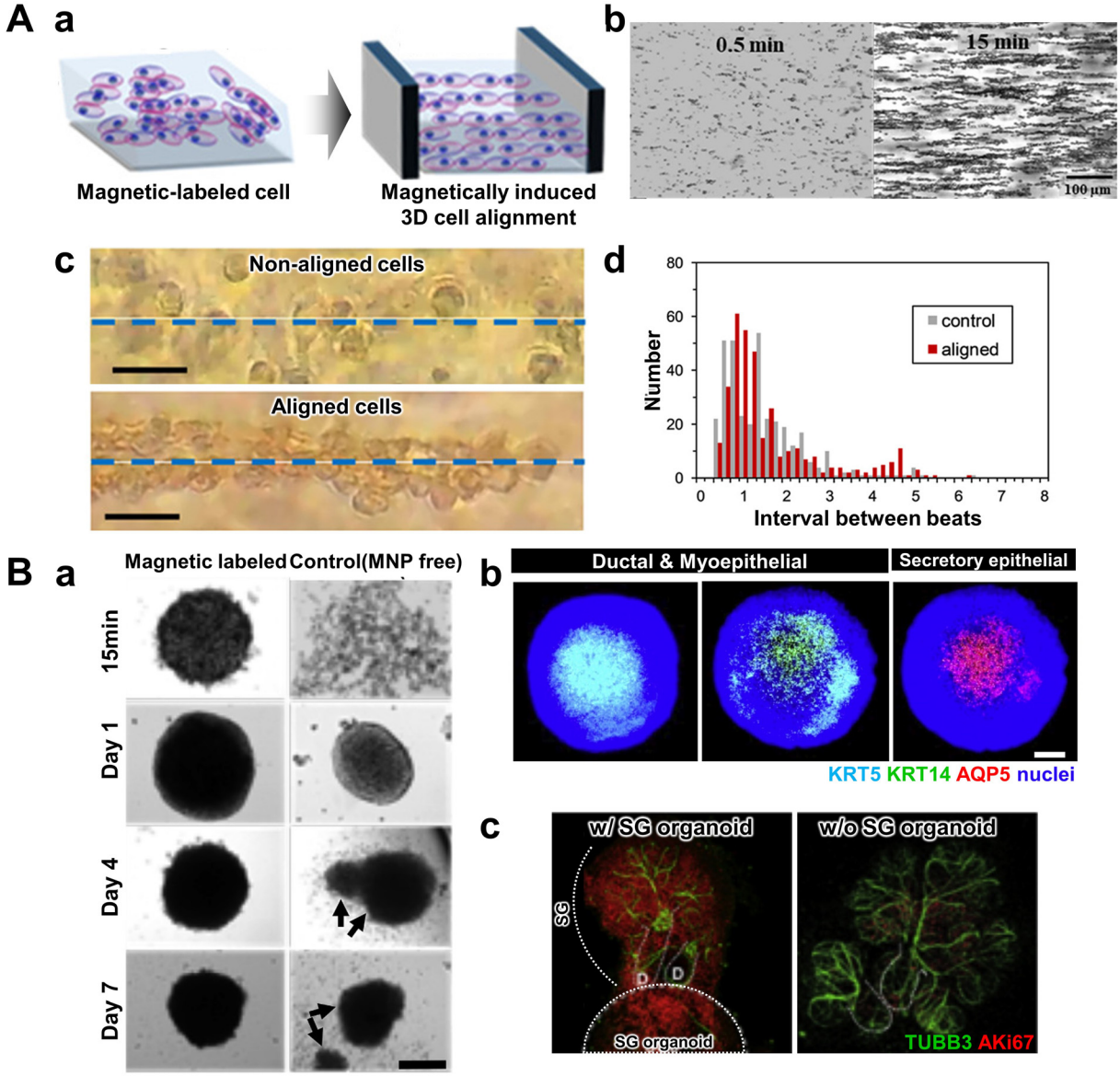

Fig. 4 Magnetic direct cell manipulation. (A-a) Schematic image of magnetically induced 3D cell alignment. (b) Cell chains of magnetic labeled cells were formatted by magnetic field. (c) Comparison of non-aligned and aligned cell chains. (d) The aligned myocardial tissue demonstrated more stable beating intervals. Reproduced from ref. 51 with permission from the American Chemical Society, copyright 2020. (B-a) Bright-field microscopy images of 3D spheroid formation on a magnetic platform, compared with control cultures (MNP-free), which exhibit spheroid disintegration beginning on day 4. (b) Fluorescent images of differentiated spheroids immunostained with various SG epithelial markers, including ductal and myoepithelial markers (KRT5, KRT14) and an acinar secretory epithelial marker (AQP5). (c) Representative images of mouse SG immunostained for nerves (TUBB3) and proliferative epithelial cells (Ki67), with nuclei counterstained using a nuclear dye, showing enhanced epithelial growth promoted by the transplanted organoids. Reproduced from ref. 62 with permission from Elsevier, copyright 2018.

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tissue. Compared with non-aligned cells, the aligned myocardial tissue showed demonstrated more stable beating intervals, preserving cardiac marker expression, emphasizing the potential of magnetic cellular labeling for replicating functional heart tissue (Fig. 4A-c).

Cell sheets are single-layered structures of closely adhered cells, used extensively in biomedical applications due to their stability in tissue transplantation. Unlike traditional methods, such as injecting single-cell suspensions or attaching cultured cells to scaffolds, cell sheets provide a more reliable approach for stable tissue engineering.[12,58] Furthermore, stacking multiple cell sheets creates multilayered structures used in vascularized tissues and complex biological assemblies.[59] By utilizing magnetic forces in cell sheet fabrication, higher-density cell sheets can be produced more rapidly. Additionally, cell sheets can be detached from the substrate simply by toggling the magnetic field, eliminating the need for enzyme treatments. Ishii *et al.* effectively employed magnetic cellular labeling technology to create cell sheets for therapeutic angiogenesis *via* cell transplantation.[60] Mesenchymal stem cells (MSCs), which are multipotent cells capable of differentiating into osteoblasts, chondrocytes, adipocytes, and smooth muscle cells, can secrete factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and stromal cell-derived factor-1α upon transplantation, promoting vascular formation within tissues. To facilitate this, the MSCs were labeled through endocytosis of magnetite (Fe_3O_4) nanoparticles. Using magnetic fields, the researchers patterned the magnetized MSCs into densely packed cell sheet forms. Compared with unmagnetized MSCs, magnetized MSCs exhibited higher cell density and produced uniform, compact cell sheets. The magnetic field-induced alignment enhanced cell–cell interactions, accelerating cell sheet formation. The increased cell density further led to significantly elevated VEGF expression levels and enhanced angiogenic capability.

Spheroids, as 3D cell culture models, emulate natural cell–cell interactions by allowing cells to adhere to one another and maintain a three-dimensional structure during cultivation. Traditional spheroid fabrication methods rely on the natural aggregation of cells, which can be time-consuming and inconsistent.[61,62] In contrast, the application of concentrated magnetic fields enables magnetic-labeled cells to assemble rapidly in three dimensions, resulting in more efficient spheroid formation. Magnetic spheroids, in particular, can be generated much faster than non-magnetic ones, as the magnetic particles within the cells are immediately attracted to specific locations. This process yields spheroids with a uniform size and shape, less affected by variations in cell density or culture conditions. Furthermore, magnetic spheroid fabrication platforms, designed for compatibility with well plates, minimize experimenter variability and improve reproducibility. A unique advantage of magnetic spheroids lies in their ability to remain manipulable using magnetic fields even after fabrication.[63–66] Magnetic fields can be used to move or fix spheroids in specific locations with ease. Bowser *et al.* leveraged magnetic cellular labeling technology to mimic the hierarchical structure of the nervous system.[67] Spinal cord cells were labeled with MNPs attached to their membranes and aggregated into spheroids using magnetic fields. During the bioprinting process, these spheroids were precisely positioned within hydrogels using external magnetic fields, enabling accurate spheroid arrangement. Adjustments to the spacing and orientation of the magnetic spheroids further enhanced neurite outgrowth and the electrical activity of the neural network compared with conventional spheroids. This study demonstrated that magnetic spheroids significantly improved cell alignment and network formation, offering superior precision and efficiency.

Magnetic organoids can similarly be manipulated through precise assembly and patterning. Unlike spheroids, organoids feature more complex structures and functions, making their fabrication challenging. MagTE enables the production of magnetic organoids with high precision. Adine *et al.* utilized magnetic cellular labeling technology to rapidly fabricate innervated salivary gland (SG) organoids.[68] Human dental pulp stem cells (hDPSCs) were magnetized using a nanoparticle solution containing gold and iron oxide nanoparticles. The magnetized cells were efficiently and stably placed in ultra-low attachment 96-well plates and assembled into magnetic spheroids using neodymium magnets (Fig. 4B-a). Subsequently, fibroblast growth factor 10 (FGF10) signaling factor was introduced to differentiate the spheroid cells into ductal and myoepithelial salivary gland cell types while promoting the expression of secretory epithelial markers (Fig. 4B-b). This process successfully generated magnetic organoids containing diverse and functionally complex cell types. When implanted into damaged salivary glands in mouse models, these organoids stimulated epithelial growth and neural network regeneration, underscoring the potential of magnetic cell manipulation for therapeutic applications (Fig. 4B-c).

3.1.2. Indirect manipulation. Several indirect cell manipulation strategies that do not involve magnetic labeling have been reported, enabling precise spatial control of cells while maintaining their viability. By employing micro/nanorobot technology, indirect cell manipulation can be achieved using magnetically responsive cell carriers. In particular, magnetic micro/nanomotors can be fabricated to transport cells by coating their surfaces with hydrogels (*e.g.*, GelMA, alginate) or bioadhesive layers (*e.g.*, fibronectin, collagen). When guided by external magnetic fields, these motors can deliver multiple cells simultaneously to specific locations, potentially facilitating the formation of complex structures at sites of tissue damage. To enhance functionality, these magnetic motors are frequently designed in a helical shape, which provides a larger surface area compared with spherical configurations, thereby accommodating more cells. The helical geometry also enables more efficient and precise movement in three-dimensional fluid environments through a corkscrew motion.[69] Yu *et al.* developed helical hydrogel-based micro/nanomotors using microfluidic spinning technology, demonstrating cell attachment and proliferation under magnetic actuation and highlighting the formation of composite structures for tissue regen-

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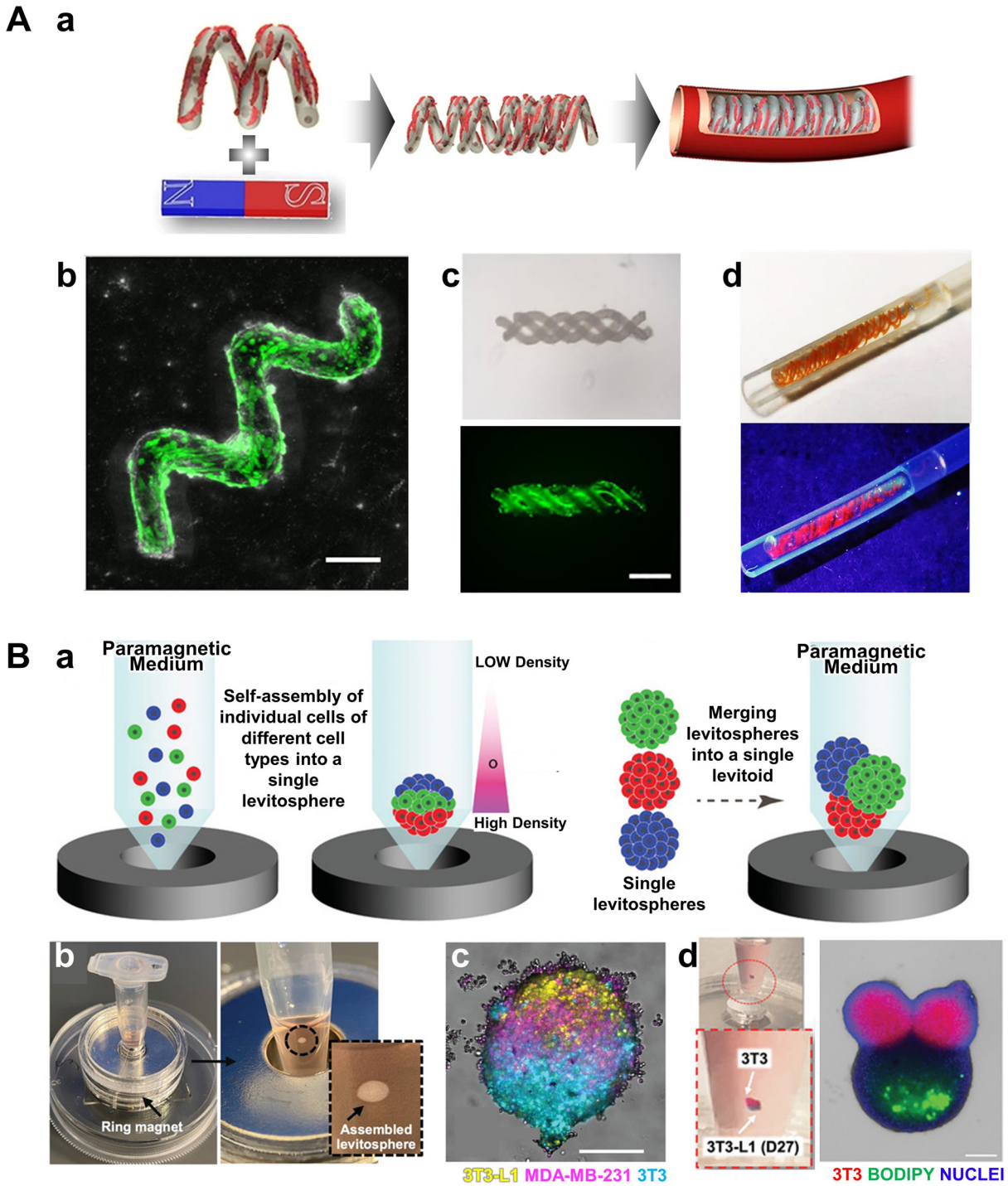

Fig. 5 Magnetic indirect cell manipulation. (A-a) Schematic image of helical micromotors as dynamic cell microcarriers. (b) Confocal laser scanning microscopy images of the helical micromotor seeded with cells. (c) Bright-field and fluorescence microscopy images of the formed triple-helical microcarriers. (d) Images of micromotor-assembled tube packed in a hydrogel and kept in a microchannel. Reproduced from ref. 64 with permission from the American Chemical Society, copyright 2020. (B-a) Schematic image of heterogeneous multicellular levitosphere and density-based spatial organization of levitospheres into levitoids under levitation. (b) Assembled levitosphere within the ring magnet-based levitation platform. (c) Fluorescent image of a heterogeneous levitosphere composed of 3T3, 3T3-L1, and MDA-MB-231 cells, showing cell positioning based on their inherent density, resulting in the formation of distinct layers. (d) Confocal image of a levitoid formed by the assembly of prefabricated 3T3-L1 and 3T3 levitospheres. Reproduced from ref. 68 with permission from John Wiley and Sons, copyright 2022.

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eration (Fig. 5A-a).[70] In this system, NIH 3T3 cells adhered to the hydrogel microcarriers by simply seeding cells in culture plates containing micromotors without requiring magnetic labeling and continued to proliferate over five days (Fig. 5A-b). Moreover, the helical design allowed these micro/nanomotors to intertwine and assemble into more complex architectures, such as double or triple helices, which could be harnessed for tissue engineering applications, particularly in repairing damaged tissues (Fig. 5A-c and d). Jeon *et al.* extended this approach by selecting human colon cancer cells as the target cells and showed that helical micro/nanomotors exhibit greater cell-loading capacity and higher motility efficiency compared with spherical ones.[71] They further demonstrated that such micro/nanomotor systems can precisely position and protect cells during transport while minimizing the need for direct magnetic labeling of the cells themselves. They verified that such micro/nanomotor systems were able to achieve precise position control and simultaneous cell protection and delivery while minimizing the magnetic labeling of the cells themselves.

Beyond magnetic spheroid formation, advanced techniques have been developed for spheroid fabrication and 3D multispheroid assembly without the need for magnetic cell labeling. These methods aim to harness the benefits of efficient 3D tissue formation through magnetic self-assembly while minimizing any potential effects of magnetic labeling on cell behavior. One such approach involves attaching magnetic particles to the surfaces of hydrogel microcapsules rather than directly labeling the cells themselves. Takeuchi *et al.* introduced a magnetic self-assembly procedure to create microstructured assemblies between toroid-shaped hydrogel microcapsules.[72] In this method, magnetic particles were affixed to the surfaces of the toroids, which were then placed in a culture dish. By applying vibrations at 80–90 rpm, the researchers successfully induced the formation of 3D multispheroid tubular structures using magnetic forces. Hepatocytes were encapsulated within the hydrogel capsules to preserve their viability and function. The assembly process was optimized through the application of magnetic fields and vibration, allowing the structures to demonstrate functional hepatocyte characteristics, including albumin secretion and urea synthesis. This approach confirmed the feasibility of creating high-density cell aggregates while avoiding direct contact between magnetic particles and the cells.

Another technique, magnetic levitation, involves adding paramagnetic salts to the culture medium, enabling cells to float based on density differences in the presence of a magnetic field. In this floating state, cells align at the point where the forces of the magnetic field and gravity balance, naturally forming uniform 3D spheroids through cell–cell interactions. Unlike magnetic spheroids, which typically require single cells and uniform structures, this method allows for the hierarchical assembly of spheroids composed of multiple cell types, leading to the spontaneous formation of multilayered structures.[73] Moncal *et al.* advanced this concept by developing a levitoid—a levitated spheroid assembly with a hierarchical arrangement (Fig. 5B-a and b).[74] They first assembled various cell types (3T3, MDA-MB-231, 3T3-L1) into a multicellular structure called a levitosphere using magnetic levitation (Fig. 5B-c). Within the levitosphere, cells naturally layered according to density differences, based on cell type, resulting in a precise layer-by-layer arrangement (Fig. 5B-d). Additionally, the team then combined the levitospheres, each with a different cell composition, to form more complex 3D structures referred to as levitoids. By using magnetic forces to design the 3D tissue assemblies and spatial organization of cells, they presented an innovative approach for fabricating multicellular structures with complex architectures. A summary of these studies is provided in Table 1.

3.2. Magnetic stimulation

When an external magnetic field interacts with magnetic particles, it can induce various physical effects, such as magnetic force, torque, vibration, and oscillation. These effects depend on factors such as the intensity and form of the magnetic field (*e.g.*, static or dynamic), as well as the type, size, and shape of the magnetic particles. Through these interactions, magnetic particles can apply mechanical, thermal, or biochemical stimulation to cells or tissues, triggering specific physiological responses. In this way, magnetic particles facilitate cell stimulation by delivering precise, non-invasive stimuli; when applied to magnetically labeled cells or magneto-responsive scaffolds, the resulting forces and motions can regulate cell growth and differentiation, enhance drug delivery, and support tissue formation.

3.2.1. Mechanical stimulation. Cells detect external physical signals—such as stiffness, shear force, and pressure from the extracellular matrix (ECM)—and respond to their environment through mechanotransduction.[75] This process converts external mechanical signals into intracellular biochemical signals. As a result, the cytoskeleton is reorganized, growth factor secretion increases, transcription factors are activated, and cell–cell adhesion is strengthened, ultimately promoting cell differentiation, maturation, and tissue formation. In the body, mechanical stimuli are naturally provided by blood flow and interstitial fluid, which support cellular maturation and development. Therefore, various methods have been devised for mechanical stimulation in cell and tissue culture.[76,77] By utilizing magnetic particles, mechanical stimulation can also be applied in engineered environments. This is achieved by incorporating MNPs into the ECM or scaffold surrounding the cells. When static or dynamic magnetic fields are applied, the MNPs exert consistent or changing mechanical forces on the cells, thereby inducing changes in cell behavior.

Cells sensitive to mechanical stimulation, such as endothelial cells (ECs) and mesenchymal stem cells (MSCs), respond rapidly to these forces by maturing or secreting factors necessary for angiogenesis and tissue regeneration. Mechanical stimulation delivery methods can be broadly classified into two categories: (1) directly magnetizing the cells (magnetically labeled cells) to pull or rotate the cells with magnetic fields, and (2) magnetizing the scaffold (magneto-respon-

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Table 1 Summary of magnetic cell manipulation

Manipulation type	Magnetic particle type	Constructed structure	Primary function	Author	Ref.
Direct manipulation	Maghemite nanoparticles	3D cardiomyocyte chains	Enhance contraction strength and functional heart tissue replication	Richard *et al.*	57
	Magnetite nanoparticles	Mesenchymal stem cell sheets	Therapeutic angiogenesis through VEGF expression enhancement	Ishii *et al.*	60
	Magnetic nanoparticles	Spinal cord spheroids	Mimic neural hierarchy for improved neurite outgrowth and neural network activity	Bowser *et al.*	67
	Gold and iron oxide nanoparticles	Innervated salivary gland organoids	Stimulate epithelial growth and neural network regeneration in damaged salivary glands	Adine *et al.*	68
Indirect manipulation	Magnetic nanoparticles	Helical hydrogel-based micro/nanomotors	Enable cell attachment, proliferation, and composite structure formation for tissue regeneration	Yu *et al.*	70
	Magnetic nanoparticles	Helical micro/nanomotors	Improve cell-loading capacity, motility efficiency, and precise cell positioning during transport	Jeon *et al.*	71
	Ferrite microparticles	3D multispheroid tubular structures	Create high-density cell aggregates while preserving hepatocyte viability and function	Takeuchi *et al.*	72
	Gadolinium salts	Layered multicellular 3D levitoids	Achieve precise layer-by-layer assembly of multicellular structures for complex 3D tissue engineering	Moncal *et al.*	74

sive scaffold) to deform the scaffold with magnetic fields, indirectly transmitting forces to the cells.

In the first approach, cells respond directly to the magnetic field, which makes it easier to construct microtissues, such as cell aggregates and organized structures. In the second approach, the deformation of the scaffold generates compressive, tensile, and shear forces on the cells, promoting tissue regeneration in a 3D environment. Yang *et al.* magnetically labeled cells and assembled them into 3D microtissues using external magnetic fields.[78] By applying additional magnetic fields, they provided mechanical stimulation to these microtissues. The shapes of the microtissues were deformed, and during deformation, cell proliferation was maintained and angiogenesis was promoted. Similarly, Abdel Fattah *et al.* explored a method for guiding tissue development through localized mechanical stimulation using MNPs.[79] Traditional *in vitro* models are limited in their ability to accurately replicate the native biological environment because they only permit uniform external stimulation. To address this limitation, the research team developed magnetoids, which are magnetically responsive organoids created by incorporating magnetically labeled cells that generate mechanical forces in specific regions (Fig. 6A-a). Within the magnetoid, cells containing magnetic nanoparticles responded to an external magnetic field, causing morphological changes in designated directions (Fig. 6A-b). This interaction resulted in F-actin rearrangement and cytoskeleton remodeling. Applying a magnetic field facilitated the asymmetric growth of the tissue, promoting the formation of structured patterns essential for shaping tissue morphology and function (Fig. 6A-c). This study demonstrates that magnetic nanoparticle-mediated mechanical stimulation is a powerful tool for selectively controlling specific regions within cells, offering a novel approach for tissue engineering and regenerative medicine.

An example of the second approach is described by Manjua *et al.*, who applied physical deformation to magnetically actuated scaffolds using external magnetic fields.[80] This mechanical stress on MSCs led to an increased secretion of physiologically active molecules, such as VEGF, and promoted the creation of vascularized 3D tissues. Spangenberg *et al.* aimed to support cartilage and bone tissue regeneration by developing magnetic hydrogel scaffolds capable of providing mechanical stimulation through magnetic deformation.[81] They created magnetic inks by mixing magnetic microparticles (Fe_3O_4, 25% w/w) with alginate (alg) and methylcellulose (MC) to fabricate magnetically actuable scaffolds using 3D bioprinting techniques. They confirmed that the scaffolds deformed under external magnetic fields and found that adjusting the strand distance and scaffold design allowed for fine-tuning of the degree of deformation during stimulation. This demonstrated the potential to develop systems that could provide appropriate mechanical stimulation when cells are incorporated into the scaffolds. Wei *et al.* used magnetic fields to simulate the effects of mechanical forces and curvature on alveolar epithelial cells.[82] They created a platform that applied the desired curvature and mechanical forces to a single-layered lung epithelium (Fig. 6B-a). By fabricating magnetically active PDMS (MagPDMS) films containing NdFeB particles, they created a hammock-shaped culture platform. When magnetic fields were applied using electromagnets, the scaffold deformed, inducing mechanical stimulation (Fig. 6B-b). The curvature of the hammock scaffold promoted the formation of a single-layered small airway epithelial cell (SAEC) epithelium and mechanical responses, confirming that dynamic stimulation through magnetic activation enhanced cell proliferation and cytoskeletal reinforcement (increased expression of F-actin and cytokeratin) (Fig. 6B-c). Thus, mechanical stimulation using magnetic particles offers several advantages over traditional physical stimulation devices. It is less invasive and allows for precise spatiotemporal control. As a result, magnetic stimulation is expected to play an increasingly important role in tissue engineering and regenerative medicine in the future.

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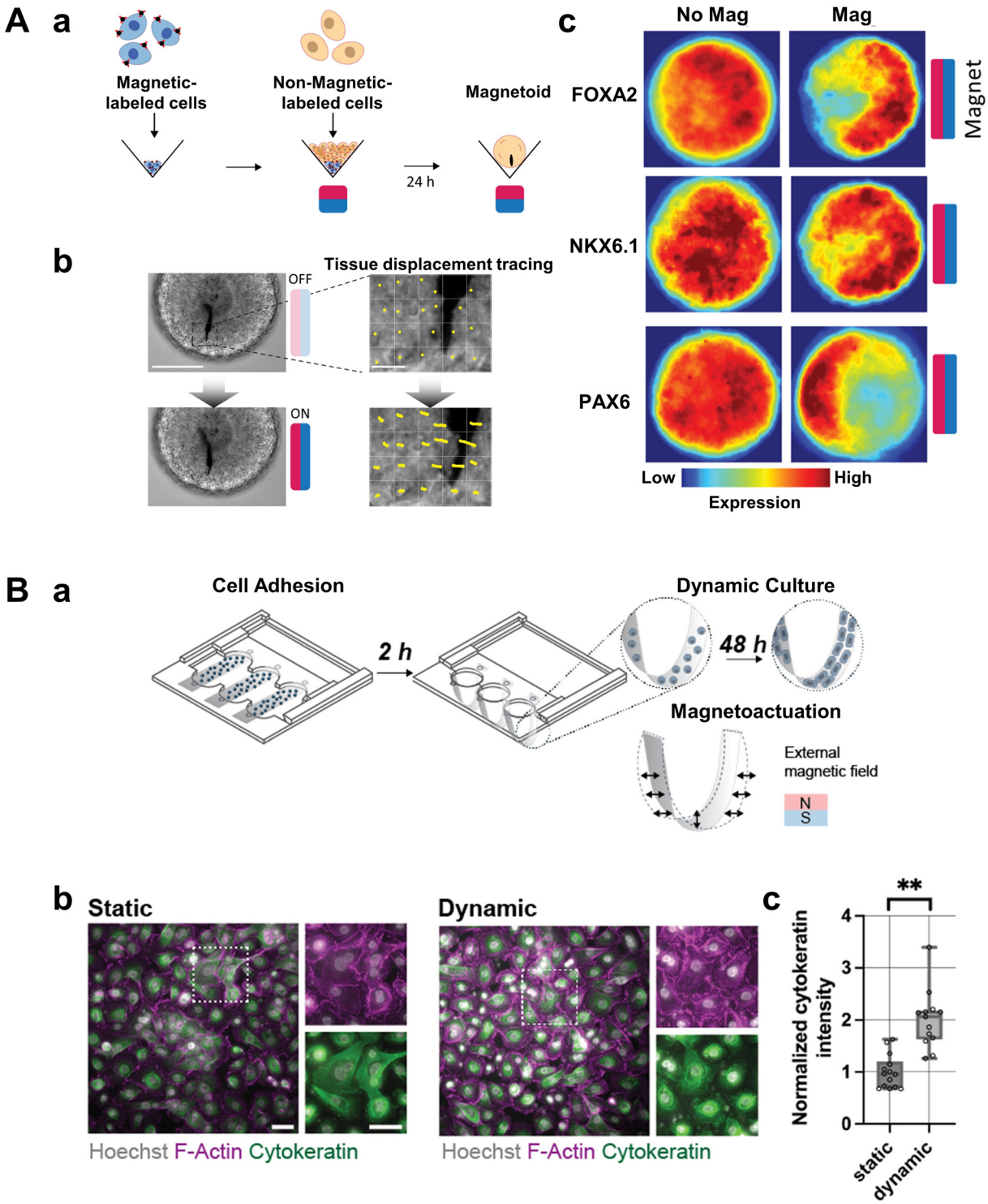

Fig. 6 Magnetic mechanical stimulation. (A-a) Schematic image of magnetoid generation. (b) Schematic representation of tissue displacement, along with tissue tracing measurement images and the corresponding heatmap. (c) Integrated fate expressions in scaled organoids, color-coded by expression frequency. Pattern formation of FOXA2 (ventral floor plate marker), NKX6.1 (intermediate domain marker), and PAX6 (dorsal marker) is induced in neural tissues. Reproduced from ref. 73 with permission from Springer Nature, copyright 2023. (B-a) Schematic image of the engineered hammock-shaped platform, featuring polyethylene terephthalate (PET) membranes secured onto a sliding hammock holder, specifically designed to fit into individual media-filled wells of a well plate. (b) Representative images of F-actin and cytokeratin in SAECs cultured under static and dynamic actuation conditions, showing enhanced expression of F-actin and cytokeratin under dynamic conditions. (c) Quantification of F-actin and cytokeratin expression in SAECs cultured under static and dynamic actuation conditions, demonstrating increased expression under dynamic conditions. Reproduced from ref. 76 with permission from Springer Nature, copyright 2024.

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3.2.2. Thermal stimulation. Thermal stimulation at temperatures above 41 °C induces a variety of physiological responses in cells and tissues. For instance, mild heat (41–42 °C) promotes the expression of growth factors such as VEGF, which in turn stimulates angiogenesis, ECM remodeling, and cell maturation. At the same time, thermal stimulation activates the production of protective proteins, including heat shock proteins (HSPs), triggering heat stress responses that help alleviate cellular stress and support the repair of damaged proteins. However, exposure to temperatures exceeding 45 °C can damage cell membranes and proteins, making it a valuable strategy for selectively targeting and eliminating cancerous or pathogenic cells.

The use of magnetic particles offers a non-invasive and precise method for applying thermal stimulation. This approach is based on the principle that magnetic particles when exposed to dynamic magnetic fields, specifically alternating magnetic fields (AMF), generate heat as their magnetic moments realign. By adjusting the intensity and frequency of the magnetic field, localized heat can be generated at specific locations, reducing the risk of damage to surrounding healthy tissues while precisely targeting the desired area. This technique, known as magnetic hyperthermia, has emerged as a prominent method for providing thermal stimulation in tissue engineering and regenerative medicine. In tissue regeneration, mild heat stimulation (41–42 °C) activates hypoxia-inducible factor (HIF-1α) in cells such as osteoblasts and chondrocytes, leading to increased expression of angiogenic factors like VEGF.[83] This process promotes cell proliferation and differentiation, facilitating tissue repair and regeneration. Additionally, magnetic hyperthermia is employed in cancer treatment, bacterial infection management, and neural tissue regeneration, where it aids in tissue repair and maturation by activating key intracellular signaling pathways. Meikle *et al.* developed a magnetically controlled VEGF delivery system that uses superparamagnetic Fe_3O_4 nanoparticles functionalized with thermoresponsive poly(ε-lysine) dendrons and carboxybetaine (Fig. 7A-a).[84] This configuration allows a strong binding of VEGF and its controlled release upon exposure to an alternating magnetic field (AMF). By applying a precisely tuned magnetic field, localized heating at 42 °C triggered the collapse of the dendron structures, enabling targeted VEGF release while minimizing premature diffusion at physiological temperatures (Fig. 7A-b). Unlike conventional VEGF delivery methods, which often struggle with sustained and gradient-based release, this approach provides a non-invasive and responsive platform for growth factor administration (Fig. 7A-c). Rosenfeld *et al.* demonstrated the potential of magnetothermal stimulation as a non-invasive method to enhance nerve regeneration by utilizing the heat dissipation properties of MNPs under alternating magnetic fields (AMF).[85] Their study targeted the activation of heat-sensitive TRPV1 ion channels in dorsal root ganglion (DRG) explants, which triggered calcium influx and promoted axonal growth (Fig. 7B-a). They found that magnetothermal stimulation at physiologically relevant temperatures (around 42 °C) significantly increased neurofilament elongation and Schwann cell migration, both essential for effective nerve repair (Fig. 7B-b). Importantly, these effects were negated when a TRPV1 antagonist was introduced, as shown in Fig. 7B-c, which displays markedly reduced neurofilament outgrowth in DRG explants. This result confirms that the observed axonal elongation was specifically mediated by TRPV1 activation rather than nonspecific thermal stimulation. Unlike traditional thermal stimulation methods that rely on direct heating elements, this approach enables precise, remote, and localized heat application, thereby minimizing damage to surrounding healthy tissues. These findings highlight magnetothermal modulation as a promising, minimally invasive strategy for promoting tissue regeneration, particularly in neural repair applications. Yamaguchi *et al.* developed a magnetically controlled gene expression system using magnetite nanoparticles that generate localized heat up to 43–45 °C under an alternating magnetic field (AMF), thereby activating the heat shock protein (HSP70B′) promoter.[86] This localized heating enabled a precise and remote induction of therapeutic gene expression, specifically tumor necrosis factor-α (TNF-α), in both *in vitro* and *in vivo* cancer models. By incorporating a transcriptional positive feedback loop with a tetracycline-responsive transactivator system, they significantly amplified gene expression upon AMF exposure, resulting in enhanced cytotoxic effects in cancer cells. This system provides a non-invasive approach for spatially and temporally regulating gene expression, offering potential applications in gene therapy and regenerative medicine. Unlike traditional thermal stimulation methods that rely on direct heating elements, this technique leverages magnetic nanoparticles to generate heat locally, minimizing collateral damage to the surrounding tissues while maximizing therapeutic efficacy.

3.2.3. Electrical stimulation. Electrical stimulation of cells and tissues can induce a range of physiological responses, including the regulation of cell behavior, tissue development, and both physiological and pathological processes. This stimulation alters the membrane potential of cells by activating or inhibiting ion channels (such as sodium, calcium, and potassium channels), thereby regulating intracellular signal transduction and cellular functions. For instance, electrical stimulation can activate signal transmission in nerve cells, induce contraction and relaxation in muscle cells, and promote growth and differentiation in stem cells. In practice, electrical stimulation has proved to be an effective method for stimulating the regeneration of damaged tissues and controlling cell growth and differentiation. However, traditional electrical stimulation systems typically require external power sources and complex wiring to deliver electrical signals to target cells and tissues. This often necessitates invasive electrode implantation, which can lead to inflammatory responses, hinder patient mobility, and cause discomfort due to the electrode connections.

To address these challenges, wireless electrical stimulation technologies that leverage magnetic particles have been developed. These technologies significantly reduce invasiveness by generating local electric fields in response to external magnetic

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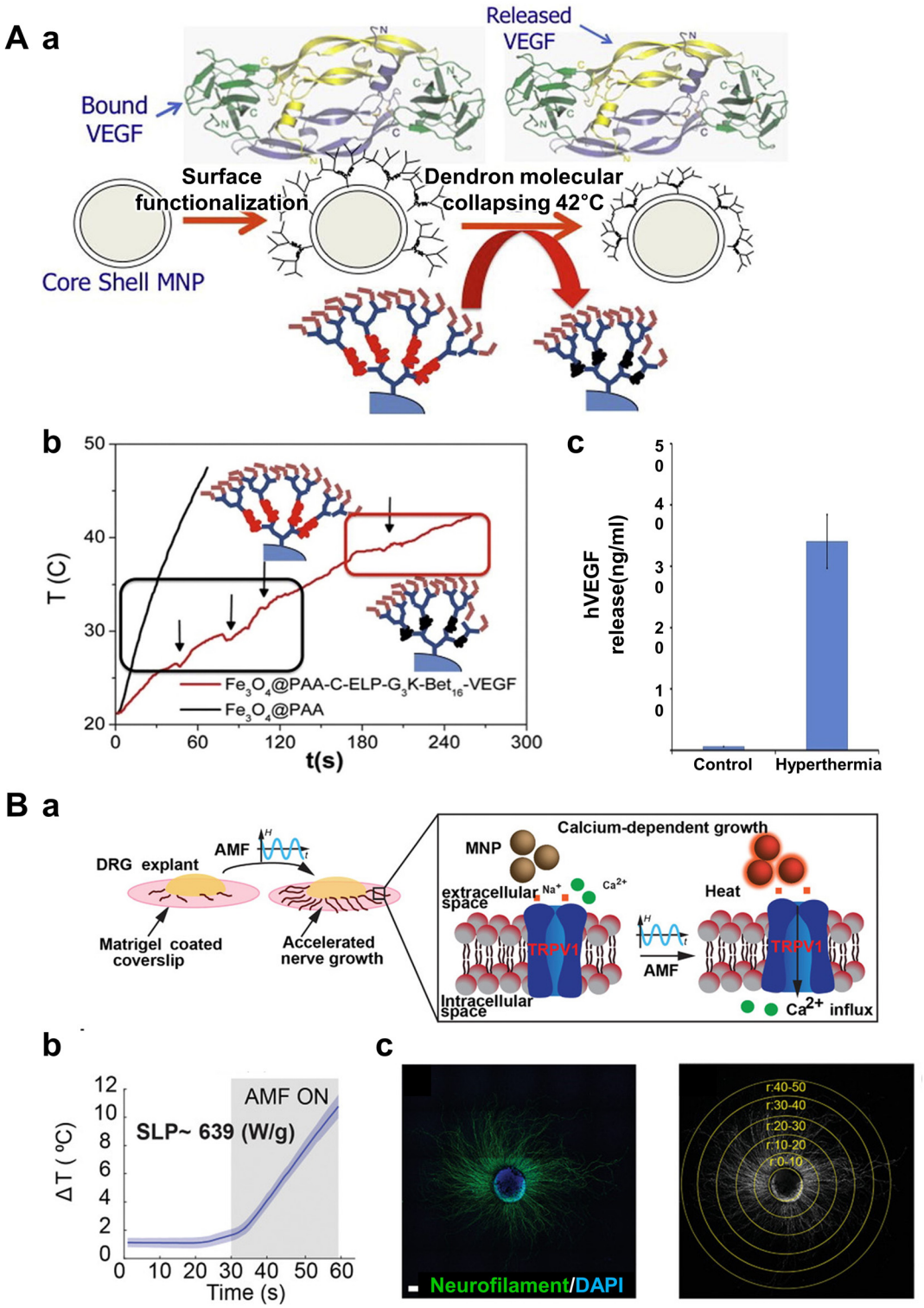

Fig. 7 Magnetic thermal stimulation. (A-a) Schematic image of surface-functionalized superparamagnetic nanoparticles conjugated with thermo-responsive poly(epsilon-lysine) dendrons, tethered with carboxybetaine, enabling mild hyperthermia-controlled delivery of VEGF. (b) A graph presenting the results of the magnetic hyperthermia experiment. The magnetic hyperthermia analysis of Fe_3O_4@PAA and Fe_3O_4@PAA-C-ELP-G3K-Bet16 demonstrated that the latter exhibited reversible structural changes (ELP oscillation and collapse) at specific temperatures, indicating its potential for temperature-controlled drug delivery and hyperthermia therapy. (c) Release of hVEGF from Fe_3O_4@PAA-C-ELP-G3K-Bet16-VEGF after hyperthermia treatment. Reproduced from ref. 78 with permission from Elsevier, copyright 2016. (B-a) Schematic image of AMF-based DRG stimulation utilizing the magnetothermal effect of MNPs to activate TRPV1 and induce calcium influx. (b) Temperature curve of MNPs in response to AMF. (c) Immunostaining and image analysis of DRGs post-stimulation, quantifying neurofilament (NF) fluorescence intensity in 50 radial locations using a confocal microscopy-based algorithm. Reproduced from ref. 79 with permission from John Wiley and Sons, copyright 2022.

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fields. The underlying principle behind this technique is magnetoelectric coupling, which combines magnetostriction and piezoelectricity. Magnetostriction refers to the property of certain magnetic materials to physically deform when exposed to a magnetic field, while piezoelectricity is the ability of certain materials to generate an electric field when mechanically deformed. For example, magnetostrictive materials like $CoFe_2O_4$ undergo magnetic domain rearrangement and physical deformation when exposed to an external magnetic field. This deformation is transferred to piezoelectric materials such as $BaTiO_3$, which then generates electric fields. These composite materials, typically consisting of a magnetostrictive core and a piezoelectric shell, are commonly known as magnetoelectric particles (MEPs).[87]

By adjusting the intensity and frequency of the external magnetic field, the magnitude and frequency of the electric signals generated by MEPs can be remotely controlled. This MEP-based wireless electrical stimulation technology allows electric fields to be delivered to cells or tissues solely through magnetic fields, eliminating the need for invasive electrode implantation and overcoming the limitations of traditional electrical stimulation systems. Qi *et al.* advanced the application of MEP-based wireless electrical stimulation by creating a scaffold embedded with $CoFe_2O_4$ (CFO) and $BaTiO_3$ (BT) nanoparticles (Fig. 8A-a).[88] Leveraging the magnetoelectric coupling effect, the scaffold generated localized electric fields in response to external magnetic fields. This wireless system effectively modulated cellular behavior, promoting cell proliferation and differentiation, and upregulating osteogenic markers such as Col-I, OCN, and Runx2 (Fig. 8A-c). Importantly, their findings confirmed that these biological effects resulted from the electrical stimulation within the scaffold rather than the magnetic field alone (Fig. 8A-b). These results highlight the potential of MEP-based wireless electrical stimulation as a non-invasive and efficient approach for tissue engineering applications, particularly in bone regeneration. Similarly, Zhang *et al.* explored the potential of MENPs for wireless neural stimulation, demonstrating that MENPs can synchronize neural activity with externally applied magnetic fields.[89] They utilized $CoFe_2O_4$@$BaTiO_3$ core–shell nanostructures to generate localized electric fields, effectively activating calcium transients and action potentials in hippocampal neurons. Furthermore, by comparing MENP-induced activation with traditional electrode-based stimulation, they confirmed that the observed neural responses were mediated by electrical signals generated by the MENPs rather than by the magnetic field alone. These findings highlight the potential of MENP-based wireless neural stimulation as a non-invasive and efficient approach for neural therapies.

3.2.4. Biochemical stimulation. Biochemical stimulation involves the delivery of bioactive substances, such as genes, proteins, and drugs, to cells or tissues to elicit specific physiological or pathological responses. In tissue engineering, this type of stimulation is vital for regulating cell behavior, promoting tissue regeneration, and initiating particular physiological processes.[90] Traditional drug delivery systems (DDS) typically involve methods such as oral administration, intravenous (IV) or intramuscular (IM) injections, and local applications. Gene delivery, in particular, has employed strategies like viral vectors, liposomes, and polymer particles.[91] Despite their widespread use, challenges persist, such as lack of target specificity, low delivery efficiency, immune responses, and the potential for gene mutations.[92] These issues have underscored the need for more efficient, precise biochemical stimulation strategies that combine biomaterials and physical stimuli.

To address these challenges, non-invasive biochemical stimulation using external magnetic fields and magnetic particles has emerged as a promising alternative. These methods generally rely on magnetic fields and particles to concentrate bioactive substances at specific target sites, such as damaged tissues. This is achieved by inducing local environmental changes—such as pH alterations, enzymatic activity, or mechanical and thermal stimuli—that trigger the release of bioactive substances precisely where needed. Magnetic field-based stimulation facilitates the accurate delivery of therapeutic agents like drugs, proteins, and genes, which are loaded onto MNPs. This method offers the advantage of precise targeting, higher efficacy, and the use of lower concentrations over shorter durations, making it especially useful in tissue engineering. First, these bioactive substances can be directly delivered to target sites using an external magnetic field. MNP surface modifications by physically or chemically conjugating growth factors or therapeutic proteins to the surface of MNPs, such as coating with polymers (PEG, PVA, PLGA), functionalization with silica (SiO_2), or conjugation with liposomes, enable the binding of various biomolecules to the MNP surface. Through these surface modifications, MNPs can effectively load chemical anticancer drugs (*e.g.*, doxorubicin, paclitaxel), proteins, and genes (plasmid DNA, siRNA).[93,94] This selective delivery method ensures the efficient accumulation of bioactive substances in damaged tissues or within deep areas of 3D scaffolds, where traditional delivery routes like blood flow are ineffective. However, simple surface modification methods have limitations in increasing drug-loading capacity or delivering multiple biomolecules simultaneously. Utilizing microcarriers made using MNPs offers several advantages over mere surface modifications. Microcarriers can increase the drug-loading capacity and allow for the simultaneous delivery of multiple bioactive molecules. Additionally, as structural supports, microcarriers maintain stable distribution within 3D scaffolds, enabling localized and sustained drug release. These advantages suggest that microcarrier-based systems can serve as more effective drug delivery vehicles in tissue regeneration and therapeutic applications. Yang *et al.* further validated this approach by developing MNP-incorporated microcarriers designed for the localized and controlled release of bioactive factors in tissue regeneration.[95] Utilizing an external magnetic field, they directed these functionalized microcarriers to specific areas within 3D scaffolds, thereby enhancing the retention and bioavailability of growth factors such as BMP2 and VEGF. This targeted delivery resulted in significant improvements in osteogenic differen-

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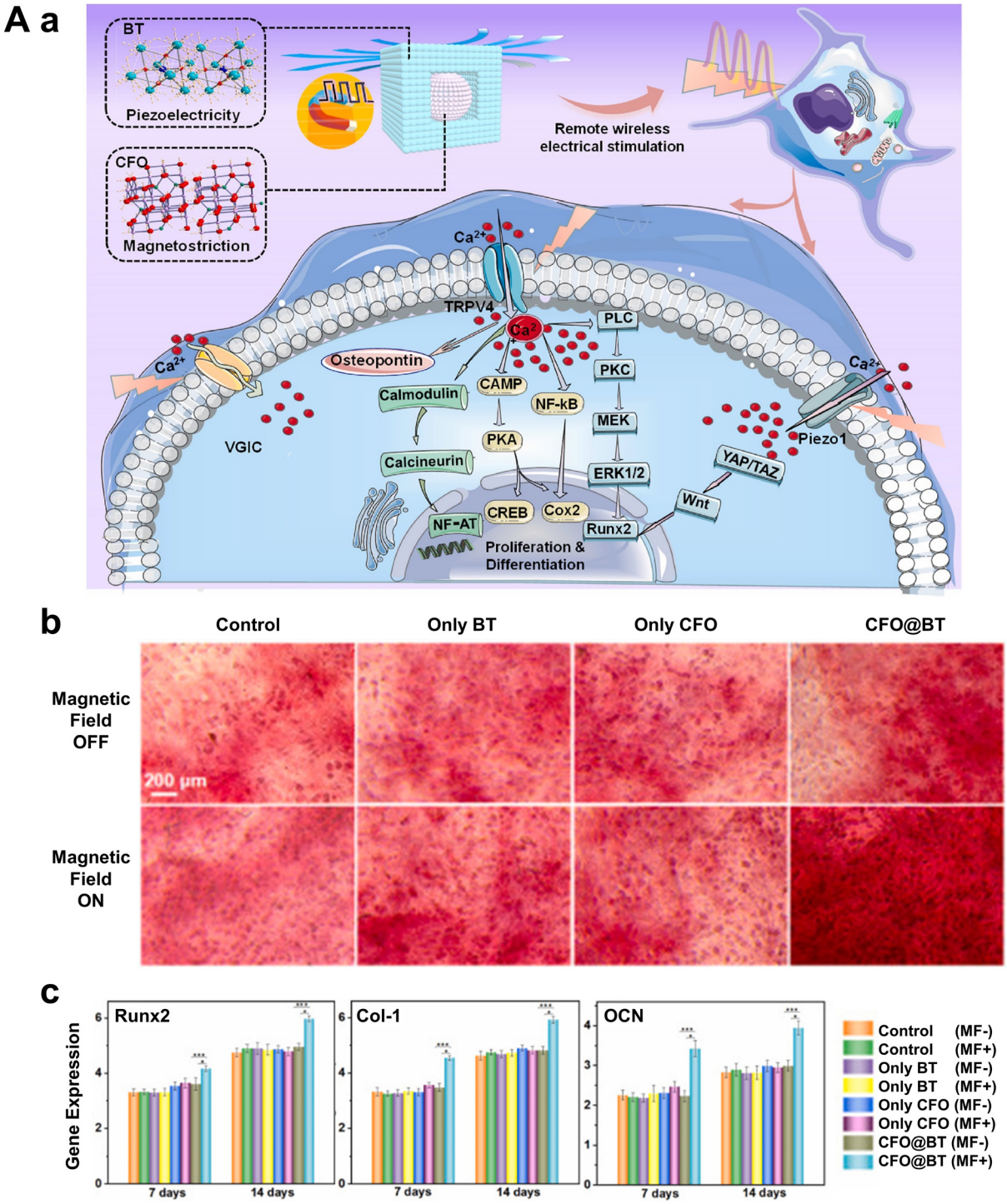

Fig. 8 Magnetic electrical stimulation. (A-a) Schematic image of magnetically driven wireless electrical stimulation within a scaffold and the proposed mechanism of remote electrical stimulation influencing cell behavior. (b) Alizarin red staining image. It shows mineralized nodules, where alizarin red binds to calcium ions through chelation, forming a fuchsia-colored complex. (c) Expression levels of osteogenic markers Runx2, Col-I, and OCN were analyzed, showing enhanced expression when both CFO and BT were present within the scaffold compared with other conditions. Reproduced from ref. 82 with permission from Elsevier, copyright 2022.

tiation and vascularization, demonstrating the potential of magnetically responsive biomaterials in regenerative medicine. Their findings support the effectiveness of magnetic targeting in overcoming the limitations of conventional drug delivery methods, providing a more efficient strategy for directing therapeutic agents to hard-to-reach tissues.

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Another notable technique is magnetofection, in which nucleic acid-loaded magnetic particles are rapidly attracted to the cell surface by external magnetic fields. This process is followed by endocytosis or other internalization mechanisms, resulting in higher gene delivery efficiency compared with conventional transfection methods. Magnetofection has proved particularly effective in cell cultures and 3D tissues, and it is especially beneficial for introducing stable genetic material into hard-to-transfect cells, such as stem or primary cells. This method shows promise for gene editing applications, including the introduction of growth factors, cytokines, and neural recovery proteins within tissues to stimulate regeneration and angiogenesis. Prosen *et al.* demonstrated the effectiveness of this approach by utilizing SPIONs functionalized with poly (acrylic) acid (PAA) and polyethyleneimine (PEI) for gene delivery into melanoma cells.[96] Their study highlighted the robustness and reproducibility of the method, as the SPION–PAA–PEI complexes efficiently bound plasmid DNA and facilitated transfection under an external magnetic field. Compared with conventional non-viral gene delivery techniques, this strategy significantly enhanced transfection efficiency while maintaining high cell viability. Heun *et al.* further advanced this concept by integrating lentiviral vectors with MNPs to achieve targeted gene delivery using an external magnetic field

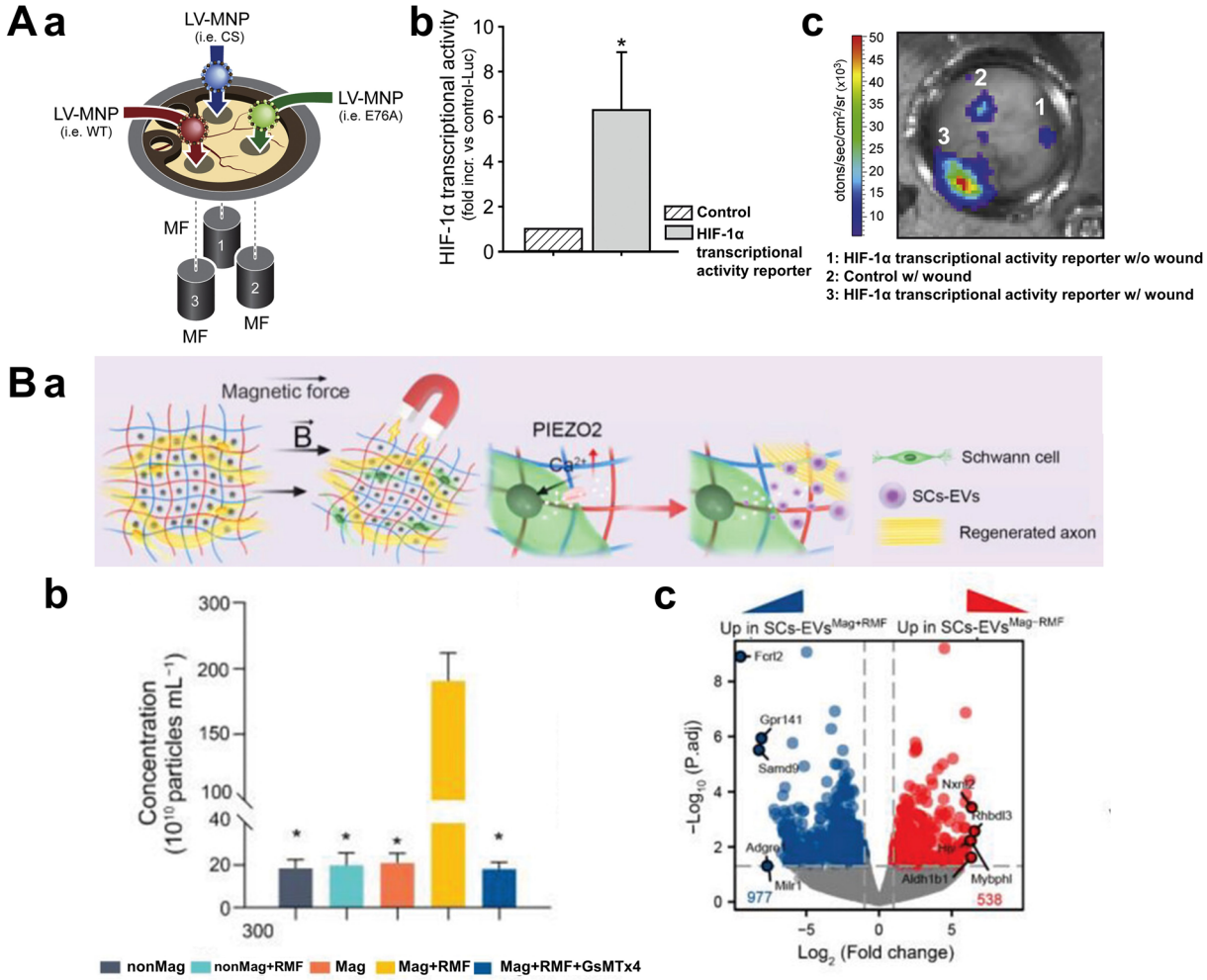

Fig. 9 Magnetic biochemical stimulation. (A-a) Schematic image of lentiviral magnetic targeting of SHP-2. Lentiviral vectors carrying expression constructs for SHP-2 mutants (WT, CS, and E76A) and HIF1-TRE-Luc were conjugated with magnetic nanoparticles and individually applied to wounds under magnetic field exposure. (b) HIF-1α transcriptional activity. HIF-1α expression and activity in wounds were assessed using a lentiviral HIF-1 transcriptional activity reporter (HIF1-TRE-Luc) and compared with control transduction. (c) The representative bioluminescence image of luciferase activity in wounds within the dorsal skinfold chamber after magnetically assisted transduction with the HIF-1α transcriptional activity reporter and control, confirming increased HIF-1α activity only in the magnetically targeted lentiviral system. Reproduced from ref. 91 with permission from Elsevier, copyright 2017. (B-a) Schematic image of magneto-mechanical actuation of encapsulated Schwann cells in Mag-gel. (b) Quantification of EVs derived from SCs with different treatments by NTA. EV secretion increased by 18.5-fold upon applying RMF to Mag-gel. (c) Volcano plot of differentially expressed genes between SCs-EVs(Mag + RMF) and SCs-EVs(Mag-RMF). Red dots indicate significantly upregulated genes in SCs-EVs(Mag + RMF), blue dots represent significantly upregulated genes in SCs-EVs(Mag-RMF), and gray dots denote non-significant changes. The results demonstrate increased expression of genes related to axon growth, angiogenesis, and inflammation regulation in EVs following magnetic field application. Reproduced from ref. 94 with permission from John Wiley and Sons, copyright 2023.

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Table 2 Summary of magnetic cell stimulation

Stimulation type	Magnetic particle type	Stimulation strategy	Target cells	Constructed structure	Primary function	Author	Ref.
Mechanical stimulation	Magnetic nanoparticles	Direct stimulation of magnetic-labeled cells	Endothelial cells	3D microtissues	Angiogenesis	Yang *et al.*	78
	Magnetic nanoparticles	Direct stimulation of magnetic-labeled cells	Human pluripotent stem cells	Magnetoid	Patterning through local mechanical forces	Abdel Fattah *et al.*	79
	Magnetic scaffolds	Deformation of magneto-responsive scaffold	Mesenchymal stem cells	Magnetic scaffold	Vascularization	Manjua *et al.*	80
	Magnetite nanoparticles	Deformation of magneto-responsive scaffold	Cartilage, bone tissue	Magnetic scaffold	Regeneration	Spangenberg *et al.*	81
	NdFeB particles	Deformation of magneto-responsive scaffold	Alveolar epithelial cells	Magnetic scaffold	Cytoskeletal reinforcement	Wei *et al.*	82
Thermal stimulation	Magnetite nanoparticles	Magnetothermal drug release	Osteoblasts, chondrocytes	Magnetic scaffold	VEGF release	Meikle *et al.*	84
	Magnetic nanoparticles	Magnetothermal drug release	Dorsal root ganglion neurons	Neural network	Axon growth	Rosenfeld *et al.*	85
	Magnetite nanoparticles	Magnetothermal gene expression activation	Cancer cells	Tumor model	Gene therapy	Yamaguchi *et al.*	86
Electrical stimulation	$CoFe_2O_4$@$BaTiO_3$ core–shell nanostructures	Wireless magnetoelectric stimulation with MENPs	Bone cells	Magnetoelectric scaffold	Osteogenic differentiation	Qi *et al.*	88
	$CoFe_2O_4$@$BaTiO_3$ core–shell nanostructures	Neural activity synchronization with MENPs	Hippocampal neurons	MENP-based scaffold	Neuronal activation	Zhang *et al.*	89
Biochemical stimulation	MNP-incorporated microcarriers	Targeted growth factor delivery	Stem cells	Microcarrier System	Growth factor delivery	Yang *et al.*	95
	SPIONs functionalized with poly (acrylic) acid and PEI	Magnetically enhanced gene delivery	Melanoma cells	Magnetic gene delivery	Transfection enhancement	Prosen *et al.*	96
	Lentiviral vectors with MNPs	Lentiviral transduction *via* magnetic targeting	Wound healing cells	Magnetic lentivirus	Angiogenesis	Heun *et al.*	97
	Gold yarn-dynamo with poly(*S*-nitrosoglutathione)	Magnetic stimulation-induced NO secretion	Neurons	Silk microneedle system	Nerve repair	Chiang *et al.*	98
	Magnetic nanoparticles	Magnetic stimulation-induced EV secretion	Mesenchymal stem cells	EV therapy system	Ischemic repair	Kim *et al.*	99
	Magnetic nanoparticles	Magnetic stimulation-induced EV secretion	Schwann cells	Magnetic hydrogel	Nerve regeneration	Xia *et al.*	100

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(Fig. 9A-a).[97] Their study demonstrated that this magnetically guided lentiviral system enabled precise, site-specific transduction, particularly in wound healing applications where HIF-1α-dependent angiogenesis was modulated (Fig. 9A-b). By leveraging magnetic targeting, they enhanced gene transfer efficiency while minimizing off-target effects (Fig. 9A-c). These findings highlight the potential of magnetically enhanced viral and non-viral gene delivery methods in regenerative medicine, offering improved precision and efficacy for therapeutic applications.

Therapeutic agents donors can also be loaded into magnetically responsive hydrogels or micro/nano-scaffolds. By applying alternating magnetic fields (AMF) or static magnetic fields, these materials can undergo shape or volume changes or increase in temperature, enabling controlled drug release at specific times. Such systems are advantageous in tissue engineering as they can simultaneously provide mechanical stimulation (through scaffold deformation) and biochemical signals (*via* drug release), broadening their applications in areas like angiogenesis and neural regeneration. For instance, when nitric oxide (NO) is bound to MNPs, exposure to an external magnetic field can trigger heating or vibration, releasing NO in a spatiotemporal manner at desired locations. Chiang *et al.* demonstrated the potential of magnetically controlled NO release for neural regeneration by developing a wirelessly chargeable gold yarn-dynamo (GY) system integrated into a silk microneedle platform.[98] Their study utilized alternating magnetic fields (AMF) to induce localized heating and electrical stimulation, thereby triggering the on-demand release of NO from poly(*S*-nitrosoglutathione) (pGSNO) donors. This method effectively promoted neurogenesis and angiogenesis while reducing inflammatory responses in a traumatic brain injury (TBI) model. By integrating mechanical, electrical, and biochemical cues within a single system, they provided a non-invasive strategy for enhancing neural repair, highlighting the versatility of magnetically responsive biomaterials in regenerative medicine.

Additionally, extracellular vesicles (EVs) represent another promising application for magnetically controlled drug release platforms. EVs play pivotal roles in intercellular communication and are rich in beneficial proteins and miRNAs derived from stem cells or immune cells which aid in tissue repair and regeneration. Several studies have explored the use of magnetic particles to encapsulate EVs or load magnetic particles into cells, allowing for the concentration of EVs under magnetic fields at high densities. This approach offers a safer and more convenient alternative to cell therapies. Kim *et al.* utilized MSCs encapsulating MNPs to generate magnetic EVs, enhancing targeting precision and therapeutic effectiveness for ischemic lesions.[99] Xia *et al.* reported that applying mechanical stimulation to Schwann cells within a magnetically responsive hydrogel scaffold induced EV secretion, thereby promoting the recovery of peripheral nerve injury sites (Fig. 9B-a).[100] The magnetic scaffold, composed of polyacrylamide/hyaluronic acid hydrogel embedded with MNPs coated with PEG/polyethyleneimine (PEI), was highly sensitive to external rotating magnetic fields. Transcriptomic analysis revealed that magnetic stimulation enriched transcripts associated with axonal growth, angiogenesis, and inflammation regulation within the hydrogel, ultimately optimizing nerve regeneration *in vivo* (Fig. 9B-b and c). A summary of these studies is provided in Table 2.

4. Conclusions and outlook

Here, we have thoroughly examined the principles, applications, and prospects of MagTE within the broader context of biofabrication. By exploring the magnetic properties of various materials, the mechanisms of magnetic actuation, and the diverse applications of MagTE in cell manipulation and stimulation, we have highlighted its pivotal role in advancing tissue engineering and regenerative medicine. Our discussion has emphasized the effectiveness of MagTE in generating complex 3D structures, including cell sheets, spheroids, and organoids, through precise magnetic labeling and manipulation. Case studies, such as the alignment of cardiomyocytes to enhance contractility and the creation of vascularized tissue structures using magnetic scaffolds, demonstrate MagTE's potential to replicate and improve upon the functional complexities of natural biological systems.

One of MagTE's key strengths is its ability to simplify biofabrication processes while ensuring high precision in the arrangement of cells and scaffolds. Traditional biofabrication techniques often require labor-intensive and time-consuming steps to achieve desired cellular architectures. In contrast, MagTE utilizes magnetic fields to non-invasively and rapidly organize cells and biomaterials, significantly reducing production time and enhancing reproducibility. This streamlined approach is especially beneficial for large-scale tissue production and the fabrication of intricate 3D structures, facilitating the advancement of personalized regenerative therapies. Although the cost-effectiveness of MagTE has not yet been fully validated in practical settings, improvements in fabrication productivity and tissue quality are expected to secure significant economic benefits, further supporting the widespread adoption of MagTE-based approaches in the future. Furthermore, MagTE's versatility in providing mechanical, thermal, electrical, and biochemical stimulations *via* magnetic actuation expands its scope, enabling the creation of dynamic and responsive tissue environments that closely mimic *in vivo* conditions.

Despite these advancements, MagTE faces several challenges that hinder its broader clinical and industrial application. Most notably, concerns about the long-term biocompatibility and safety of magnetic particles remain significant. Although magnetic particles, such as SPIONs, are generally regarded as biodegradable and biocompatible, the risks of long-term accumulation and cytotoxic effects, particularly under large-scale application, remain unresolved.[101] For clinical translation, meeting stringent regulatory standards is essential, including comprehensive safety evaluations for materials with magnetic properties.[102] In addition to long-

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term biocompatibility and safety concerns, several technical bottlenecks also hinder the expansive development of MagTE technologies. A major limitation lies in the attenuation of magnetic force and torque with increasing distance, which presents a significant obstacle in scaling MagTE approaches from localized cellular to organ-level tissue constructs. The strength of a magnetic field decreases rapidly with distance; specifically, in the case of a dipole field, the magnetic field strength is inversely proportional to the cube of the distance ($\propto 1/r^3$). This steep decline makes it extremely challenging to achieve uniform and sufficient magnetic manipulation across large and thick tissue constructs. As the size of the target tissue increases, the magnetic gradient becomes weaker and more heterogeneous, making it difficult to maintain precise control over cellular alignment and scaffold deformation throughout the entire structure. Furthermore, compensating for this distance-related attenuation by applying stronger external magnetic fields may introduce additional risks of mechanical and thermal stress to cells. High-intensity magnetic fields can directly exert mechanical stress on cells, negatively impacting their viability, adhesion, and differentiation processes. Moreover, excessive magnetic hyperthermia induced by AMF could compromise the biological integrity of the engineered tissues. These challenges underscore the need for continued research to improve the properties of magnetic materials, reduce cytotoxic effects, and develop robust magnetic control systems capable of managing larger and more complex tissue constructs.

To overcome these obstacles and fully realize MagTE's potential, it is crucial to integrate it more effectively with other emerging biofabrication technologies. For example, combining MagTE with 3D bioprinting could enhance the precision and complexity of tissue structures by enabling the simultaneous magnetic manipulation and layer-by-layer deposition of cells and biomaterials. Additionally, integrating microfluidic systems with MagTE could improve the nutrient and oxygen supply within large tissue constructs, addressing the critical challenge of vascularization. These synergistic integrations are essential to overcoming current technical limitations and enabling the fabrication of physiologically relevant and clinically applicable tissues and organs.

A particularly promising yet underexplored direction for expanding MagTE's capabilities involves the use of hard magnetic particles, which are widely employed in magnetic robotics.[103,104] Unlike superparamagnetic particles that lose magnetization when the external field is removed, hard magnetic particles retain their magnetization, enabling persistent magnetic actuation even without continuous external field application.[103,104] This persistent magnetization allows for real-time and sustained control over the spatial arrangement and structural properties of tissues, supporting the fabrication of highly functional and adaptable organ models. However, challenges remain: hard magnetic particles may present biocompatibility issues due to their persistent magnetization, potentially leading to undesirable interactions and cytotoxicity as previously discussed. Notably, unlike superparamagnetic materials—which generally exhibit minimal cytotoxicity when embedded in polymeric matrices—hard magnetic particles such as NdFeB have demonstrated concentration-dependent cytotoxic effects even without external magnetic field exposure. These adverse effects, however, were substantially mitigated by applying biocompatible polyelectrolyte surface coatings, emphasizing the critical role of interface engineering in minimizing unintended interactions with biological components and preserving tissue architecture.[105] Additionally, integrating them into biofabrication workflows requires advanced magnetic control systems that can precisely guide and modulate these particles without compromising tissue integrity. The nonlinear dynamic behaviors of hard-magnetic structures—such as undesired vibrations or positional instability under time-varying magnetic fields—can compromise the spatial accuracy of cell patterning and alignment during biofabrication. These effects necessitate the integration of closed-loop control strategies, such as PID controllers, to ensure reliable and precise actuation throughout the tissue assembly process in biomedical applications.[106] To address these challenges, future efforts should focus on the development of biocompatible hard magnetic materials, refinement of particle size and surface properties to reduce cytotoxicity, and the engineering of adaptive control systems optimized for organ-scale constructs. In parallel, comprehensive studies on their long-term behavior and safety in biological environments will be essential for advancing clinical translation.

In conclusion, MagTE has demonstrated remarkable capabilities in cellular manipulation and tissue formation, providing a strong foundation for next-generation biofabrication technologies. By addressing existing limitations through integration with complementary biofabrication tools and exploring the untapped potential of hard magnetic particles, MagTE is well-positioned to revolutionize the creation of complex, functional artificial tissues and organs. These advancements will not only address pressing clinical challenges but also drive the evolution of precision medicine, ultimately leading to the development of innovative therapeutic solutions and improved patient outcomes.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

Conflicts of interest

There are no conflicts to declare.

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