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REVIEW

Nanomaterial-Mediated Stem Cells Fate Regulation: From Mechanism of Action to Regenerative Medicine Applications

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Abstract

Stem cells possess self-renewal capacity and differentiation potential. Under appropriate conditions, they can continuously divide to generate more stem cells of the same type or differentiate into various specialized cell types, thereby contributing to the formation of diverse tissues and organs. In tissue engineering and regenerative medicine, stem cells serve as key elements for repairing or replacing functional tissues lost due to disease, injury, or aging. The development of nanomaterials has provided new tools and approaches for stem cell research, particularly in the biomedical field, where they are widely applied in drug delivery, biosensing, medical imaging, and tissue engineering. Moreover, through interactions with cell membranes and/or intracellular components, nanomaterials can modulate key stem cell functions — including differentiation, proliferation, and adhesion — thereby enhancing the therapeutic efficacy of stem cells in biomedical applications. This review first introduces the main characteristics and potential risks associated with the application of nanomaterials to stem cells. The subsequent section provides an overview of how nanomaterials regulate stem cell biological functions and activate associated signaling pathways, followed by a discussion of future directions and challenges in this field.

Keywords

Nanomaterials; Stem cells; Regenerative medicine; Signaling pathways

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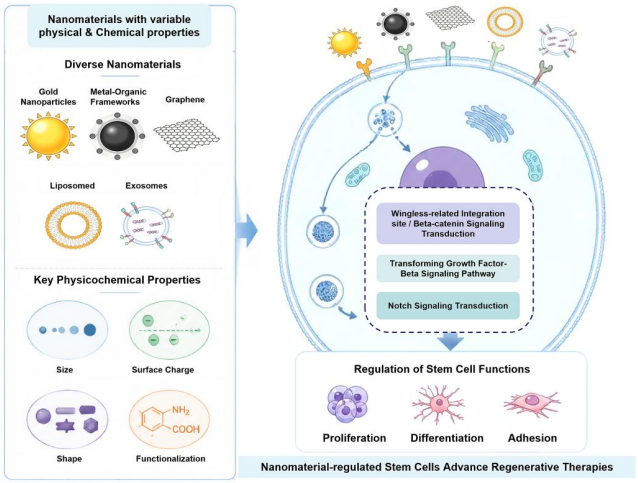
Graphical Abstract



Highlights

- Tunable physicochemical properties make nanomaterials ideal stem cell modulators.
- These materials dictate stem cell fate by optimizing the local microenvironment.
- Targeted modulation of critical signaling pathways steers stem cell behaviors.

1. Introduction

Stem cells have shown great potential in regenerative medicine and disease treatment due to their ability to self-renew and differentiate into multiple cell types. Stem cells can be divided into two types according to their differentiation potential, such as pluripotent and multipotent stem cells, as shown in the **Figure. 1**[1,2]. Among them, the most studied stem cells include embryonic stem cells (ESCs), induced pluripotent stem cells (iPSCs), bone marrow mesenchymal stem cells (BMSCs) and adipose-derived stem cells (ADSCs)[3,4]. These cells can differentiate into various tissue cells in the body, such as neurons, liver cells, cardiomyocytes, through specific signalling pathways and gene regulatory mechanisms. In clinical practice, stem cells have been used to treat various diseases, such as bone marrow transplantation for blood diseases, mesenchymal stem cell therapy for tissue damage[5,6].

In the context of stem cell regenerative medicine, the term “nanomaterials” encompasses a broad spectrum of nanoscale structures. This includes not only rigid, solid nanoparticles (e.g., metallic and ceramic particles) and extended nanostructures (e.g., nanotubes and nanosheets), but also soft, vesicular nanocarriers such as liposomes and cell-derived exosomes. Rather than being restricted to a strict solid-state definition, these diverse nanoscale platforms are unified by their capacity to interface with stem cells, deliver bioactive cargoes, and structurally or chemically modulate the cellular microenvironment. Nanomaterials are promising for applications in marker tracking, drug delivery, cell imaging, and modulation of stem cell function due to their small size, easy surface modification, good biocompatibility, and remote activation.

The combination of stem cells and nanomaterials has found three main applications: enabling stem cell tracking and imaging, facilitating gene regulation to enhance directed differentiation, and serving as carriers for precision targeted delivery. Despite the numerous challenges that remain, such as biocompatibility and long-term safety issues, the future of this approach in regenerative medicine and disease therapy is undeniably promising. As technology progresses and research deepens, this interdisciplinary field will undoubtedly contribute even greater benefits to human health.

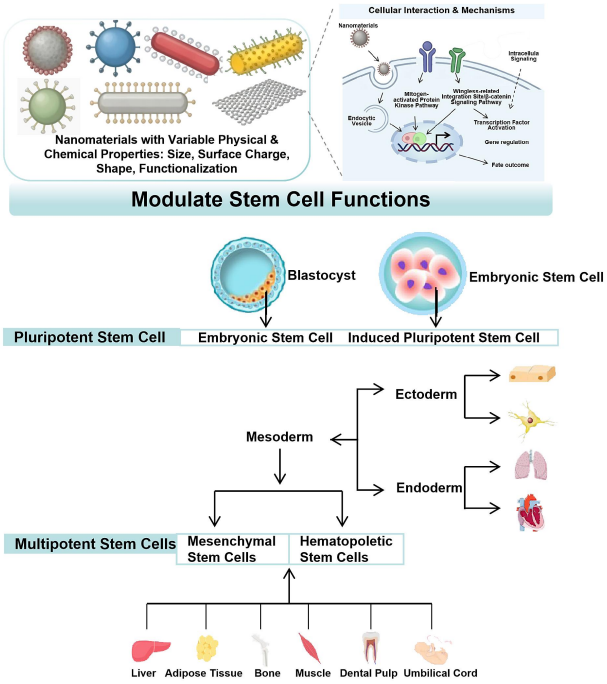


Figure. 1 Regulation of stem cell function by nanomaterials. Created by the author using Microsoft PowerPoint.

2. Key Properties of Nanomaterials for Stem Cell Applications

2.1 High Specific Surface Area

The small size of nanoparticles provides a high specific surface area, enabling them to capture and adsorb abundant active molecules or proteins in body fluids. This alters their surface properties, enhances biological activity, and increases the likelihood of cellular interactions[7,8]. Consequently, nanoparticles can more readily cross cell membranes and enter cells to influence cellular functions.

Two-dimensional nanomaterials (such as graphene and transition metal oxide nanosheets) and highly porous metal-organic frameworks (MOFs) also exhibit a remarkably high specific surface area. The abundant surface atoms and unique structural properties of these nanomaterials provide high surface energy and versatile anchoring sites[9,10]. For instance, the oxygen-containing functional groups and π-π conjugated domains on graphene oxide, or the defect sites on transition metal oxides, can readily adsorb extracellular matrix (ECM) proteins (such as fibronectin or vitronectin) from biological fluids[11,12]. This non-covalent adsorption alters protein conformation to expose specific binding epitopes, such as the Arg-Gly-Asp (RGD) sequence. These exposed epitopes serve as potent ligands that specifically recognize and bind to cell-surface integrins (such as α5β1 or αvβ3). Such integrin-mediated interactions trigger focal adhesion formation and activate downstream signaling pathways, thereby significantly enhancing cell adhesion, spreading, and subsequent cellular functions[13].

Furthermore, the flexible coordination chemistry between metal nodes and organic linkers enables the mild, in situ construction of MOF architectures driven directly by biomolecules. Rather than acting merely as passive guests, biomolecules possess abundant surface functional groups (e.g., amine, carboxyl, and thiol moieties) that actively recruit and concentrate metal ions via electrostatic and coordination interactions. This local enrichment significantly lowers the activation energy for nucleation, thereby acting as the primary thermodynamic and kinetic driving force to guide the self-assembly of the MOF shell [14]. This bio-driven coordination chemistry ensures that biomolecules are efficiently incorporated into structurally stable host–guest complexes, protecting the active biological cargo while maintaining high adsorption capacity [15,16]. For instance, when antioxidant nanoenzymes drive the biomimetic mineralization of MOFs, the resulting H_2O_2-responsive MOFs can subsequently release the nanoenzymes in lesion areas, promoting targeted differentiation of neural stem cells and facilitating nerve regeneration [17]. Looking forward, exploiting biomolecules as structural driving forces offers profound projections for nanomedicine. Future developments are expected to transition toward constructing multi-compartmental or dynamically responsive Bio-MOFs that emulate natural organelles, thereby enabling highly precise cell-interfacing biohybrid materials and cascade-reaction delivery platforms.

However, the high specific surface area also tends to cause nonspecific adsorption, particularly for porous nanoparticles. When biomolecules diffuse to the particle surface, the lack of effective antifouling or selective recognition capabilities may lead to nonspecific adsorption, which can hinder target molecule diffusion into interior pores, cause pore blockage, and reduce both adsorption efficiency and selectivity. To address this, researchers have developed various strategies. For instance, constructing ideal coatings on magnetic gold nanoparticles using zwitterionic polymers significantly reduces nonspecific adsorption of serum proteins[18]. Alternatively, coating magnetic beads with antifouling dendritic peptides effectively resists the adsorption of nontarget biomolecules in complex biological samples, enabling highly selective recognition[19]. Other studies have modulated the conformation and density of polyethylene glycol (PEG) chains to create a stealth shield in the open pore regions of porous nanoparticles, thereby reducing cellular interactions and nonspecific adsorption[20]. Notably, nonspecific adsorption not only compromises detection sensitivity and reproducibility but may also accelerate the clearance of nanodrug carriers in vivo, limiting their clinical translation. Therefore, when designing porous nanomaterials with high specific surface area, it is essential to optimize pore structure and incorporate surface antifouling functionalization to balance adsorption capacity and selectivity.

2.2 Biocompatibility

Biocompatibility is a critical consideration in biomedical material development. With the rapid emergence of artificial nanomaterials, their biosafety and biocompatibility have gained increasing importance. Many nanoparticles exhibit good biocompatibility, enabling interaction with biological tissues and cells without significant immune responses or toxicity. Biocompatibility can vary with size, composition, morphology, surface modification, and surface charge. Among carbon nanoparticles, fullerenes demonstrate better biocompatibility than single-walled and multi-walled carbon nanotubes[21]. Metal and semiconductor nanoparticles generally exhibit lower biocompatibility compared to carbon-based counterparts[22,23], while metallic nanoparticles (e.g., gold nanoparticles, superparamagnetic iron oxide) show concentration-dependent biocompatibility[24]. In addition to solid polymeric and inorganic nanoparticles, soft nanoscale vehicles — such as liposomes and exosomes — are widely utilized as highly biocompatible nanomaterials. Commonly used biocompatible polymeric materials include poly (lactic acid) (PLA), poly (glycolic acid) (PGA), poly (lactic-co-glycolic acid) (PLGA), and poly (vinyl alcohol) (PVA). Owing to their excellent biocompatibility, these FDA-approved materials are widely used for biodegradable nanoparticles[25]. For instance, amphiphilic block copolymers can self-assemble into polymeric vesicle nanoparticles featuring hydrophobic layers and aqueous cavities. Leveraging their good biocompatibility and ability to preserve bioactivity, these nanoparticles enable stable cellular uptake and promote cell proliferation, offering a therapeutic approach for liver injury in mouse models. Additionally, nanoparticles with a polymer coating exhibit enhanced biocompatibility and are more readily internalized into mesenchymal stem cells (MSCs) without affecting their natural function[26].

Among various nanocarriers, liposomes stand out for their non-toxicity and biocompatibility, making them ideal for human studies. Liposomes can be used for stem cell labeling. For example, biocompatible nanoprobes composed of liposome-indocyanine green hybrid vesicles have been employed to label human mesenchymal stem cells. The study by Mazza *et al.,* showed that the labeled stem cells were transplanted as spheroids into subcutaneous and intracranial regions of athymic nude mice, enabling cell tracking via imaging systems for up to two weeks (subcutaneous) and one week (intracranial)[27]. Additionally, liposomal nanocarriers protect encapsulated therapeutic agents from chemical and biological degradation, with degradation

products being fully biocompatible and metabolizable. Particularly in cancer stem cell research, liposomal carriers can be co-loaded with multiple therapeutic agents and modified with tumor-specific surface ligands, allowing these versatile nanocarriers to modulate physicochemical properties, immunological mechanisms, and uptake pathways to achieve antitumor effects[28].

In recent years, exosomes — natural nanovesicles with excellent biocompatibility and transport properties — have been widely applied in tissue engineering for cell-free therapy. They avoid the immune rejection associated with cell-based approaches while performing cell-like functions. Stem cell-derived exosomes are rich in bioactive contents that regulate intercellular communication. For instance, mesenchymal stem cell-derived exosomes promote the in vitro expansion of hematopoietic stem cells (HSCs) while preserving their stemness[29]. Moreover, exosomes can be engineered to deliver therapeutic agents such as immunomodulators, drugs, and antisense oligonucleotides, enabling effective regulation of recipient cell functions and participation in various physiological and pathological processes[30]. Notably, Xu *et al.,* demonstrated that targeted delivery of small-molecule drugs to MSCs via engineered exosomes results in uniform cytoplasmic drug dispersion and effectively promotes chondrogenesis both in vitro and in vivo[31].

To further improve the biocompatibility of engineered nanoparticles for clinical translation, several advanced strategies must be considered. Surface functionalization with stealth polymers, such as polyethylene glycol (PEG) or zwitterionic ligands, effectively reduces nonspecific protein adsorption and delays immune clearance. Furthermore, biomimetic engineering, such as camouflaging nanoparticles with host-derived cell membranes (e.g., erythrocyte or stem cell membranes), offers a robust approach to evade immune surveillance while maintaining high biological safety[32,33]. Additionally, precisely tuning the physicochemical properties (e.g., size and surface charge) and optimizing the degradation kinetics of polymeric carriers are critical steps to minimize intracellular toxicity and prevent long-term tissue accumulation[18,20].

2.3 Controlled Release

Compared with traditional carrier systems, nanocarriers offer enhanced efficacy due to their unique size, shape, and material properties. Currently, nanoparticle-based innovative drugs have become a major research focus in nanobiomedicine. Nanoparticles can deliver a wide range of cargoes, including nucleic acids, peptides, proteins, radioactive agents, chemotherapeutic drugs, photosensitizers, and fluorescent probes.

To achieve better controlled release, stimuli-responsive nanocarrier systems have gained increasing attention. These nano-assemblies maintain structural stability under normal conditions and undergo conformational changes or chain cleavage upon reaching target sites or receiving external stimuli, enabling spatiotemporally controlled substance release[34]. This capability is particularly valuable in stem cell regenerative medicine, where precise regulation of stem cell biological functions is essential.

Common responsive release triggers include pH, temperature, and light. pH-responsive nanocarriers exhibit good colloidal stability and significant pH-dependent release behavior. For example, Bahadori *et al.,* developed a three-component polysaccharide-based nanocarrier that achieved controlled release of curcumin, with accelerated release under acidic conditions (pH 5.4) and slow release under neutral conditions (pH 7.4) [35].

Temperature-responsive systems offer another controlled release strategy. Liu *et al.,* designed temperature-responsive hollow mesoporous silica nanoparticles grafted with poly (N-isopropylacrylamide) as a molecular gate. Below the lower critical solution temperature, the polymer chains extend, opening the mesopores to allow small molecule entry. Above this temperature, the chains collapse, blocking the channels and encapsulating the cargo. This simple temperature-based switching enables precise control over drug loading and release, providing an efficient strategy for intelligent drug delivery systems[36].

Additionally, Li *et al.,* developed a receptor-responsive nanoparticle that exploits the urokinase receptor (uPAR) on cancer cells to trigger degradation. In the presence of uPAR within the tumor microenvironment, nanoparticles specifically binding to this receptor disintegrate into 7.5 nm fragments and release their cargo. These nanoparticles exhibit enhanced uptake by uPAR-expressing cancer cells in vitro and demonstrate higher cytotoxicity, showing promise for tumor stem cell elimination [37].

2.4 Targeting

Precision nanomedicine is an emerging field offering unique opportunities for diverse biomedical applications. Notably, nanoparticles with precise targeting capabilities have been developed to overcome biological barriers, enhance drug accumulation in specific tissues and cells, and prolong circulation time[38]. Ideally, nanoparticles should avoid clearance by the mononuclear phagocyte system and maintain prolonged circulation to ensure adequate target tissue accumulation and internalization. Improving nanoparticle targeting thus remains a key research direction.

Surface functionalization with specific ligands — such as antibodies, small molecules, or sugar groups — enhances affinity for target cells, enabling targeted stem cell delivery and precise manipulation. For instance, engineered extracellular vesicle vectors incorporating RNA aptamers against epithelial cell adhesion molecules (a liver cancer stem cell marker) can specifically bind liver cancer stem cells and deliver β-catenin-targeting RNA therapeutics to achieve effective killing[39]. Similarly, gold nanoparticles (AuNPs) can be readily modified with ligands, drugs, or biocompatible coatings to construct nanobioconjugates with tumor-targeting agents such as antibodies for active targeting of lung cancer stem cells[40].

Active targeting employs external stimuli like magnetic fields, light, or ultrasound to guide nanoparticles to specific sites. For example, pulsed-wave Doppler ultrasound can regulate nanobubble movement speed, propelling and guiding oxygen nanobubbles to tumor hypoxic regions for precise drug delivery[41]. Leveraging stem cell-specific biological interactions for active targeting has also gained traction. Utilizing the inherent tumor-homing and migratory properties of mesenchymal stem cells (MSCs), researchers have developed genetically engineered MSC membrane-derived nanoparticles with high CXC receptor 4 (CXCR4) expression, enabling active migration to injury sites and enhanced tissue penetration to promote cartilage repair[42].

Passive targeting exploits the enhanced permeability and retention (EPR) effect of tumor tissues, allowing appropriately sized and surface-charged nanoparticles to accumulate preferentially in pathological regions. Cancer stem cells exhibit a propensity for retaining small particles, making nanoparticles promising for chemotherapeutic delivery. Studies show that small

polymeric nanoparticles (< 12 nm) can target tumors via the EPR effect; PEGylated nanoparticles below 12 nm exhibit minimal nonspecific uptake, whereas larger ones tend to accumulate in major organs, leading to prolonged circulation and potential toxicity[43]. Additionally, nanoparticles capable of charge switching in response to tumor acidity represent an effective EPR-based delivery platform. These particles remain neutral at physiological pH 7.4 for stealth circulation but switch to a cationic state under acidic tumor conditions, enhancing tissue interaction and tumor accumulation. The positive net charge further enables greater accumulation in more acidic hypoxic regions, achieving targeted delivery to the hypoxic tumor microenvironment[44].

2.5 Optical and Magnetic Properties

Certain nanoparticles possess unique optical and magnetic properties that enable cell imaging and tracking, allowing real-time monitoring of stem cell distribution and behavior in vivo. Among them, gold nanoparticles (AuNPs) and silver nanoparticles (AgNPs) with plasmon resonance properties are widely used in imaging systems for targeting and imaging of small molecules, DNA, proteins, tissues, and tumors. For instance, embedding AgNPs into microbubbles creates dual-mode ultrasound and optical imaging probes, with AgNPs significantly improving ultrasound contrast[45].

AuNPs are readily applicable for enhanced optical imaging due to their plasmon resonance properties, including absorption, scattering, fluorescence, and Raman scattering. In a skin burn repair model, AuNP-labeled adipose-derived mesenchymal stem cells (ASCs) were implanted into a polyethylene glycol-fibrin gel scaffold, and photoacoustic imaging clearly distinguished transplanted stem cells from host tissue without affecting ASC network formation or growth factor secretion[46,47]. Recently, a second near-infrared window probe/bioluminescence imaging has overcome limitations of low tissue penetration and precision, enabling deep-tissue stem cell tracking. Combined with Raman imaging, this approach achieves high-resolution molecular and cellular analyses, with star-shaped AuNPs and Ag_2S quantum dots serving as biocompatible dual-modality contrast agents for signal amplification[48].

Magnetic particle imaging is an emerging cell tracking technique offering advantages such as radiation-free operation, high signal-to-noise ratio, zero signal attenuation, and high sensitivity. However, its utility is limited by the lack of optimal magnetic nanoparticle tracers. Ideal tracers should exhibit monodispersity, high saturation magnetization, high magnetization, and weak coercivity. By tuning shape and size to optimize magnetization and cellular internalization, very low concentrations (30 cells/μL) of labeled MSCs can be detected, with in vivo sensitivity reaching up to 2,500 cells regardless of tissue depth[49].

Beyond tracking and imaging, magnetic nanoparticles (MNPs) exhibit targeting and magnetothermal properties under magnetic fields. For example, loading hydrophilic MNPs into liposome lumens enables magnetic targeting under external fields [50]. MNPs can also convert magnetic energy into heat to control drug release or kill tumor cells. One study reported multifunctional magnetic liposomes loaded with doxycycline that rotate at high speed in high-frequency magnetic fields, increasing membrane permeability and drug release rates[51].

Long-term application of nanomaterial tracers in vivo raises concerns about accumulation and toxicity. To address this, researchers have developed degradable live-cell fluorescent tracers based on photoluminescent poly (citrate-siloxane) nanoparticles. These tracers are efficiently internalized by cells, enabling selective lysosomal imaging with high photostability, and support adipose-derived mesenchymal stem cell labeling for up to 14 days or more, offering a safe option for long-term live-cell imaging without toxicity concerns[52].

2.6 Toxicity Risk

The cytotoxic effects of nanoparticles are highly dependent on their physicochemical properties and experimental conditions, including size, shape, surface charge, solubility, coating, concentration, raw material, exposure time, and target cell type.

For instance, AuNPs exhibit size-dependent cytotoxicity: smaller particles (1.4 nm) are more cytotoxic and induce necrosis, whereas larger particles (> 1.4 nm) typically induce apoptosis[53,54]. Surface charge also plays a critical role; charged gold nanoparticles induce apoptosis, while neutral nanoparticles trigger necrosis[55]. Similarly, cationic nanocarriers induce acute cell necrosis via interaction with Na^+/K^+-ATPase, leading to mitochondrial damage-associated inflammatory responses [56].

Accumulation of nanomaterials in the body can adversely affect physiological functions, including toxicity and immune reactivity. For example, alumina nanoparticles exert neurotoxic effects and may contribute to aluminum accumulation in neural tissues, potentially inducing Alzheimer's disease[57]. Nanoparticles can also engage immune cells such as neutrophils and macrophages, triggering inflammation. Prolonged inhalation of copper oxide nanoparticles has been shown to alter immune cell composition and reactivity[58]. To prevent accumulation, degradable nanomaterials are often used; however, their degradation products may pose new challenges. For instance, degradation of PLA, PGA, and PLGA can lead to local accumulation of acidic metabolites, acidifying the microenvironment and affecting cellular behavior[59].

Regarding toxicity mechanisms, reactive oxygen species (ROS) are a common pathway. AgNPs typically exhibit genotoxic effects by inducing ROS generation, leading to DNA damage[60,61]. AuNPs at certain concentrations also induce ROS production upon cellular entry, resulting in oxidative stress-associated cytotoxicity, including DNA damage, apoptosis, necrosis, and cell cycle arrest[62]. Notably, some studies have leveraged toxicity for therapeutic benefit; AgNPs can accumulate in tumor tissues and trigger mitochondrial dysfunction, oxidative stress, autophagy, and various cell death pathways, offering a promising strategy for eliminating cancer stem cells[63,64].

Future research should focus on reducing toxic effects through improved nanomaterial synthesis strategies — such as surface modification, structural design, biomolecular conjugation, and concentration control — while addressing nanomaterial stability and potential immunological risks.

3. Nanomaterials for Stem Cell Function Regulation

The stem cell niche is a specialized local microenvironment that physically anchors stem cells and provides essential biochemical and biophysical cues to govern their fate. Nanomaterials exert a profound effect on this niche by acting as engineered components of the artificial ECM. Through precise nanotopography and tunable mechanical stiffness, nanostructured substrates can structurally mimic the native niche architecture, thereby regulating cytoskeletal tension and integrin-mediated mechanotransduction. Furthermore,

nanomaterials can dynamically remodel a pathological niche by scavenging excessive local reactive oxygen species (ROS) or by creating localized, sustained concentration gradients of morphogens (such as TGF-β or Wnt ligands). By intervening at the niche level rather than solely targeting the stem cells themselves, nanomaterials establish a highly optimized, pro-regenerative microenvironment that tightly orchestrates stem cell adhesion, self-renewal, and localized differentiation.

3.1 Stemness Maintenance

Stemness maintenance refers to preserving the self-renewal capacity and undifferentiated state of stem cells, maintaining necessary differentiation genes at balanced expression levels[65]. This process is critical for stem cell function and application, determining whether stem cells can consistently generate identical progeny capable of differentiation when needed. Compared with ESCs, bone marrow MSCs, and neural stem cells (NSCs), human adipose-derived stem cells (hADSCs) are abundant, readily available, have low immunogenicity, and can be isolated from excess adipose tissue with minimal harm[66]. However, despite their abundance, hADSCs require expansion to meet therapeutic demands. During long-term in vitro culture, stem cells gradually lose directional differentiation capacity and undergo spontaneous differentiation, with stemness loss being the primary cause. This loss represents a major limitation to the clinical application of stem cells[67]. Conventional stemness maintenance relies on growth factors or drugs, but their high cost and susceptibility to degradation restrict their application[68]. Recently, nanomaterials have emerged as a cost-effective strategy for maintaining stemness in tissue engineering.

In addition to primary tissue-derived MSCs, induced pluripotent stem cell-derived MSCs (iPSC-MSCs, also termed iMSCs) have emerged as a highly scalable resource that overcomes the inherent heterogeneity and replicative senescence of conventional MSCs. Recently, nanomaterials have shown great promise in maintaining the distinct biological characteristics and regulating the molecular functions of iMSCs. For instance, engineered nanostructured substrates and functionalized nanocarriers can effectively preserve their youthful phenotype, robust immunomodulatory capacity, and paracrine activity during extensive in vitro expansion. Furthermore, specific nanomaterials can precisely guide the targeted differentiation of iMSCs by modulating key intracellular signaling cascades, highlighting a promising avenue for standardized regenerative therapies[69,70].

To overcome the limitations of growth factors or drugs, nanomaterials offer an effective approach by encapsulating key bioactive factors into biodegradable nanoparticles for targeted delivery, enabling spatially and temporally localized paracrine stimulation. For example, encapsulating biofactors in biodegradable liposomes and targeting cell surfaces with antibodies against oligosaccharide antigens enables sustained release and dynamic microenvironmental control to maintain stemness[71].

Certain nanomaterials themselves also regulate stemness. Studies show that zinc oxide (ZnO) nanoparticles effectively maintain hADSC stemness during expansion. Zn^{2+} release from ZnO nanorods enhances Krüppel-like factor 4 *(KLF4)* gene expression, promoting *OCT4* and *NANOG* expression critical for stemness maintenance[72]. Beyond nanoparticles, nanosheet materials such as Ti_2CT_x — a transition metal carbide/nitride/carbonitride with graphene-like properties — exhibit excellent hydrophilicity and significant advantages in maintaining MSC stemness, as shown in the **Figure. 2**[73].

Combining materials with external stimuli, such as piezoelectricity, can also maintain NSC stemness. For instance, electrospun poly (L-lactic acid) (PLLA) nanofiber membranes with piezoelectric properties maintain NSC stemness under piezoelectric vibration-driven local electrical stimulation without neural proliferation factors[74].

Extracellular vesicles (EVs) have emerged as important nanovesicles mediating intercellular communication and can substitute for stem cell functions. A novel stemness maintenance mechanism involves ectodermal cells maintaining the blastocyst microenvironment via secreted exosomes to prevent premature differentiation. Neural stem cell exosomes regulate NSC stemness; proteomic analyses reveal differential expression of EV proteins between proliferative and quiescent states. Regulating these protein expression levels can maintain NSCs in a quiescent state, thereby preserving stemness[75]. ESCs generate abundant EVs containing fibronectin molecules, promoting multivalent interactions with integrins on target ESC surfaces to activate the FAK pathway and maintain stemness[76]. However, the precise molecular mechanisms underlying nanomaterial- or nanotechnology-mediated regulation remain incompletely elucidated, representing a key direction for future research.

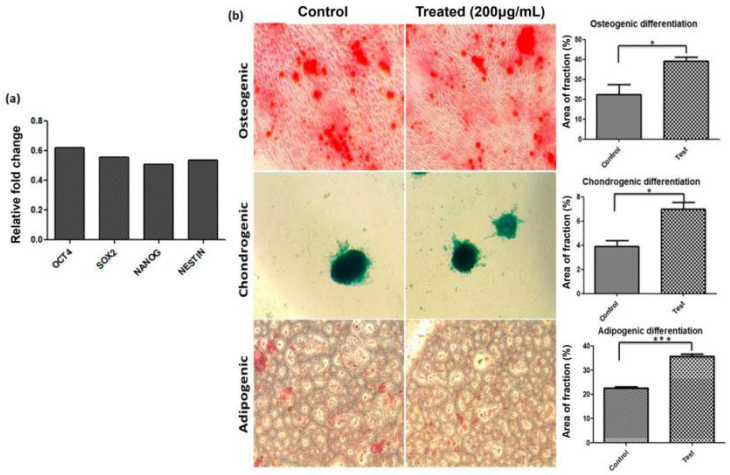


Figure. 2 Nanomaterials maintain stem cell stemness[73]. (a) Expression of stemness marker, (b) Phase contrast microscopic images and gene expression analysis showing the enhanced tri-lineage differential potential of mesenchymal stem cells with the nanosheet. (* p-value < 0.05; *** p-value < 0.001). Copyright© 2022 Suraj Kumar Singh, Anshuman Singh, Vinod Kumar, Jalaj Gupta, Sima Umrao, Manoj Kumar, Devojit Kumar Sarma, Marcis Leja, Manohar Prasad Bhandari, and Vinod Verma.

3.2 Proliferation and Survival

In stem cell therapy, cell survival is critical, as stem cells must persist in injured tissues to exert paracrine effects. Mechanical lysis, apoptosis, and oxidative stress can lead to rapid cell death, causing extensive clearance of transplanted cells and limiting therapeutic efficacy. Nanomaterials can promote stem cell survival and proliferation by delivering drugs/genes or improving the culture environment [77,78].

Researchers applied poly-β-aminoester nanoparticles containing CXCR4 gene plasmid DNA to ADSCs in vitro and found that these nanoparticles enhanced ADSC engraftment by regulating gene expression and prolonged cell survival in ischemic limb muscles[79].

Environmental regulation represents another effective strategy for promoting stem cell proliferation. For instance, removing reactive oxygen species (ROS) from the stem cell microenvironment can protect cells and enhance their activity. In Mn-Co_3O_4, the Co sites exhibit an increased Co^{2+}/Co^{3+} ratio and improved redox performance, enhancing ROS clearance efficiency. This effectively protects hMSCs from ROS attacks, reverses apoptosis, and rescues functions such as adhesion, spreading, proliferation, and osteogenic differentiation [80].

Cerium oxide nanomaterials with different morphologies exhibit distinct ROS-scavenging mechanisms. Short nanoparticles and nanorods are rapidly internalized, whereas long nanowires are internalized slowly, leading to differences in intracellular distribution. Compared with long nanowires, short nanomaterials more effectively alleviate intracellular damage — including DNA fragmentation, lipid peroxidation, and protein degradation — thereby better preserving stem cell proliferative capacity [81].

The size and concentration of nanoparticles can also directly affect cell proliferation. For example, 60 nm AuNPs at a concentration of 56 μm significantly promote the proliferation of human periodontal ligament stem cells, as shown in the **Figure. 3**[82]. Multiple signaling pathways are closely associated with cell proliferation, including SMAD, Notch, FGF, Hedgehog, and Wnt. Studies have shown that AuNPs can activate lipoprotein receptor-related protein 5 (*LRP5*) and β-catenin, thereby activating downstream stem cell proliferation-related genes such as *MYC*, *CCND1*, *AXIN2*, and *POU5F1*. Thus, the regulatory mechanism of AuNPs on proliferation is closely linked to the Wnt/β-catenin signaling pathway[83].

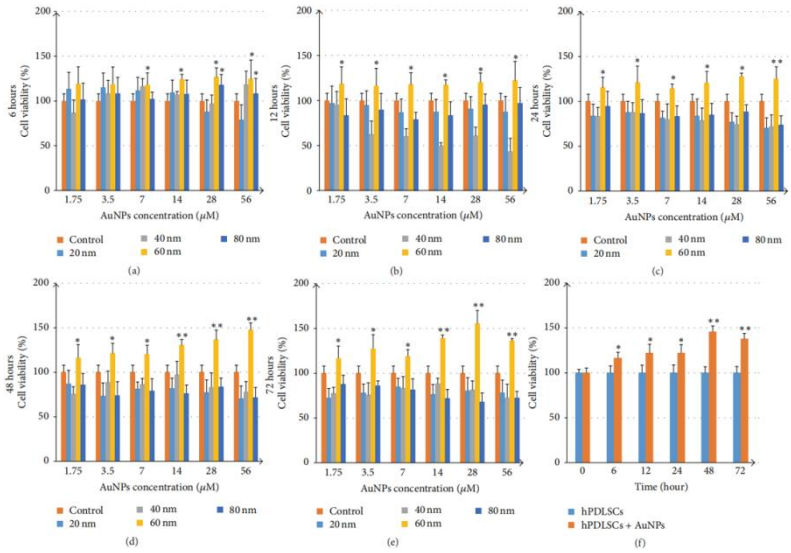


Figure. 3 Effects of nanomaterials with different sizes and concentrations on stem cell proliferation. (a)Viability of hPDLCs incubated with six different concentrations of four sizes of AuNPs for 6 h; (b) Viability of hPDLCs incubated with six different concentrations of four sizes of AuNPs for 12 h; (c) Viability of hPDLCs incubated with six different concentrations of four sizes of AuNPs for 24 h; (d)Viability of hPDLCs incubated with six different concentrations of four sizes of AuNPs for 48 h; (e) Viability of hPDLCs incubated with six different concentrations of four sizes of AuNPs for 72 h; (f) Proliferation and viability of hPDLSCs in the presence of 60 nm AuNPs (56 μM) for 6, 12, 24, 48, and 72 h (* p-value < 0.05; ** p-value < 0.01) [82]. Copyright© 2016 Chen Li, Zhuoquan Li, Yan Wang, Hongwei Liu.

3.3 Differentiation

The clinical application of stem cells primarily relies on regulating differentiation into specific cell types. Considerable efforts have been made to direct stem cell differentiation into osteoblasts, neurons, adipocytes, and cardiomyocytes[84-87]. However, low differentiation efficiency and success rates limit therapeutic applications. Additionally, undifferentiated ESCs post-implantation increase teratoma risk, underscoring the need for strategies that enhance targeted differentiation into specific lineages[88,89]. Nanotechnology offers promising avenues for developing nanomaterials capable of regulating stem cell differentiation. Indeed, various nanomaterials have been shown to direct differentiation into multiple cell types through distinct mechanisms[90-94].

Nanomaterials with suitable properties can regulate stem cell differentiation by modulating the intracellular environment[95]. Their physicochemical characteristics — such as size, surface charge, and shape — interact with various ligands to influence differentiation outcomes[96,97]. Nanomaterials of appropriate size can penetrate cell membranes via clathrin- and caveolin-dependent endocytosis, phagocytosis, and macropinocytosis, entering the cytoplasm and promoting differentiation[98]. Studies indicate that the optimal particle size for inducing differentiation ranges from 20 nm to 70 nm[99-101]. For example, researchers evaluated AuNPs of varying diameters (5 nm, 13 nm, and 45 nm) on human periodontal ligament progenitor cells (PDLPs). Although AuNPs of all three sizes are efficiently internalized by the cells and predominantly accumulate in intracellular vesicles, they exhibit distinct

osteogenic effects. Specifically, 5 nm AuNPs reduced alkaline phosphatase (ALP) activity, mineralization, and osteogenic gene expression, whereas 13 nm and 45 nm AuNPs increased these osteogenic markers, with the 45 nm AuNPs being more effective than the 13 nm AuNPs in promoting osteogenic differentiation, as shown in the **Figure. 4**[102]. Furthermore, autophagy activation correlated with their effects on osteogenic differentiation, indicating that AuNPs influence osteogenic differentiation in a size-dependent manner via autophagy. At equivalent sizes, cells internalize nanospheres more efficiently than nanorods. Spheres of 40 nm and 70 nm, as well as 70 nm rods, enhance ALP activity and calcium deposition, whereas 40 nm rods reduce MSC osteogenic differentiation[103].

Surface charge and functional groups also significantly impact stem cell differentiation. Introducing different chemical functional groups onto inorganic silica nanoparticles revealed that phosphate-functionalized nanoparticles upregulated osteogenic genes and induced osteoblast-like morphology[104]. Similarly, negatively charged graphene quantum dots (GQDs) were shown to enhance hMSC osteogenic differentiation by activating the BMP/Smad signaling pathway[105].

In addition, cells can perceive and respond to physical signals in their surrounding microenvironment. For instance, in magnetomechanical stimulation, researchers demonstrated the correlation between differentiation and tension by directly applying quantified magnetic force to cells. Incorporating magnetic nanoparticles (MNPs) into hMSCs enabled control of cell–matrix tension via magnetic force; as applied tension increased, the expression levels of osteogenic differentiation marker genes and proteins were proportionally upregulated[106]. Photoresponsive nanoparticles have also been developed. A near-infrared (NIR)-mediated stem cell differentiation control system based on upconversion nanoparticles (UCNPs) can release stem cell differentiation factors under 808 nm NIR excitation, guiding NSC differentiation in a highly controllable manner[107].

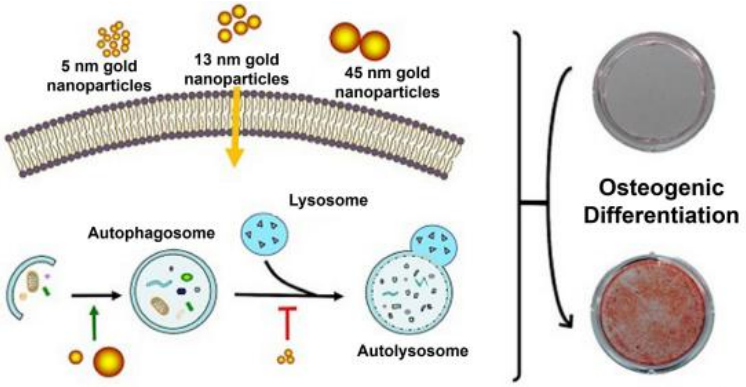


Figure. 4 Nanomaterials promote the osteogenic differentiation capacity of hMSCs[102]. Copyright© 2017 Yangheng Zhang, Na Kong, Yuanchao Zhang, Wenrong Yang, and Fuhua Yan.

3.4 Adhesion, Migration, and Homing

When cells come into contact with cells or the ECM, the initial response is adhesion. Through adhesion, cells can perceive and respond to changes in their microenvironment, thereby regulating their function and state[108,109]. Peng *et al.,* demonstrated that poly (L-lysine) (PLL) nanosheets assembled at liquid–liquid interfaces exhibit molecular weight-dependent toughness. High molecular weight PLL formed continuous, tough interfaces, whereas low molecular weight PLL produced fragile nanosheets. Despite similar initial cell adhesion, MSCs on low-toughness interfaces exhibited reduced proliferation due to cell-mediated fracture, which was prevented by myosin II inhibition. This study demonstrates that stem cells sense interfacial toughness, which regulates cell expansion, as shown in the **Figure. 5**[109].

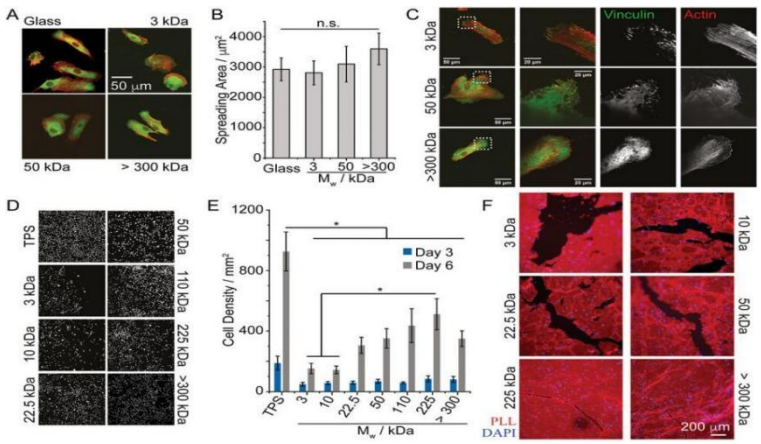


Figure. 5 Nanomaterials regulate the adhesion and spreading behavior of stem cells. (A, B) Impact of nanosheet molecular weight on MSC spreading at Novec 7500 liquid–liquid interfaces. (C) Confocal microscopy images of MSCs spreading (24 h) on nanosheet/FN-functionalized Novec 7500 interfaces. (D, E) MSC expansion on nanosheet-stabilized Novec 7500 interfaces. (F) Highly confluent MSCs remodel and fracture the nanosheets at the interface. (* p-value < 0.05) [109]. Copyright© 2023 Lihui Peng, Carlos Matellan, Minerva Bosch-Fortea, Jordi Gonzalez-Molina, Matteo Frigerio, Stefan Salentinig, Armando del Rio Hernandez, and Julien E. Gautrot.

Transmembrane adhesion proteins — including immunoglobulin superfamily cell adhesion molecules (CAMs), selectins, integrins, and other adhesion molecules — play important roles in adhesion. Integrins mediate cell–ECM connections, while adhesins link cells to other cells or tissues[110]. Adhesion molecules also play a critical role in cell migration; for instance, integrins participate in transmitting pulling and pushing forces during migration by interacting with ECM proteins[111]. Stem cell migration is fundamental to homing, which depends on specific adhesion molecules and chemokines. Stem cells reach target tissues via the circulation, and interactions between homing receptors and ligands enable localization and retention[112]. The CXCR4/CXCL12 axis, for example, not only mediates HSC homing but also regulates their retention and mobilization in the bone marrow[113,114].

A major limitation of current stem cell therapy is the limited control over stem cell functional behavior. Nanotechnology-based innovations enable effective and dynamic control of stem cell states through biophysical cues.

Nanomaterials can regulate stem cell adhesion by modifying cell membrane surfaces and altering culture substrate properties. For example, conjugating superparamagnetic iron oxide nanoparticles with adhesive ligands and adjusting integrin ligand nanoscale oscillation via magnetic field frequency enables remote magnetic control of stem cell adhesion[115]. In material modification, polyvinyl alcohol hydrogel adhesives incorporate clay nanoparticles — such as unmodified montmorillonite (MONT) and modified montmorillonite (OMONT) — as adhesion factors to overcome insufficient stem cell adhesion[116]. RNA sequencing has further elucidated the complex mechanisms of cell–interface events, revealing that hierarchical structures of hydroxyapatite (HA) micro/nanoparticles — including nanosheets, needle-like, and spherical structures — are crucial for regulating the actin cytoskeleton. Notably, sheet-like structures positively regulate cell adhesion by modulating the actin cytoskeleton[117].

Migration typically follows adhesion. Once adhered, cells generate migratory forces through complex signaling pathways and cytoskeletal dynamics. The cell front forms pseudopodia to propel forward, while the rear contracts to facilitate movement, involving coordinated actions of Rho family GTPases, actin, and myosin[118,119]. Gold nanoparticles internalized by MSCs have been reported to increase actin and microtubule protein expression levels fourfold, thereby enhancing migration rates[120].

External interventions, such as applied magnetic fields, can also direct nanoparticle-magnetized stem cells to target tissues for repair. In a rat model of ischemic brain injury, intravenous injection of superparamagnetic iron oxide nanoparticle (SPION)-labeled stem cells, combined with an external magnet (0.32 T) attached to the skull for one week, resulted in a threefold increase in the infarct area under the magnet, effectively treating cerebral ischemic infarction[121].

Poor stem cell homing and low engraftment efficiency remain major obstacles to systemic infusion. Regulating homing-related biological factors is a key strategy. One study developed alendronate-modified liposome nanoparticles for bone-targeted *SDF-1* gene delivery to stimulate stem cell migration. Alendronate facilitates bone targeting via chelation interactions between its bisphosphonate groups and calcium ions in bone minerals. Osteoblasts transfected on the bone surface secrete SDF-1 protein into the bone marrow, establishing a concentration gradient that mobilizes stem cells to the bone surface, where they differentiate into osteoblasts and contribute to bone regeneration[122].

3.5 Internalization and Absorption

Current research on particle–cell interactions has directed scientists to consider factors beyond material composition, necessitating precise design of physicochemical properties — such as size, shape, elasticity, surface charge, and surface functionalization — to achieve effective stem cell internalization[123].

Regarding nanoparticle shape, most nanomedicines in clinical trials or laboratory-scale studies are spherical. Through further research, scientists synthesized fluorescently labeled spherical polymer nanoparticles via free radical polymerization and controlled mechanical deformation to produce quasi-ellipsoidal polymer nanoparticles with varying aspect ratios. Studies on mesenchymal stem cell uptake of equal-volume spherical and non-spherical particles revealed that ellipsoids were more easily adsorbed but exhibited lower cellular uptake than spherical particles, with a negative correlation between aspect ratio and uptake rate. Considering that surface charge density changes upon stretching, Coulomb interactions favor ellipsoids with negative charges along the polar axis. Meanwhile, cells must wrap around the polar axis during uptake, leading to decreased nanoparticle internalization with increasing aspect ratio. Thus, slender nanoparticles functionalized with specific ligands are suitable drug delivery carriers, but shape-change effects should ensure restoration of the original spherical shape under external stimulation to maximize cellular uptake upon target cell recognition[124].

Additionally, researchers have found that tuning elasticity can effectively improve nanoparticle drug delivery. Softer particles may evade endocytosis, leverage blood persistence to enhance circulation and targeting, and increase binding to target sites. Conversely, if intracellular delivery and rapid internalization are required, harder particles can enhance cell interactions and uptake. Soft nanoparticles exhibit longer circulation times than hard nanoparticles over short periods, potentially because phagocytic cells (e.g., macrophages) may exert sufficient force to deform soft particles during phagocytosis. Particle elongation may increase cell membrane tension, reducing phagocytosis[125]. Compared with stiffer nanoparticles, softer particles diffuse onto the cell membrane, increasing interaction strength but raising the membrane energy barrier for complete encapsulation, making them less suitable for membrane wrapping[126].

Surface modification of nanoparticles has enabled the design of imaging nanoparticles that specifically bind to cell surface receptors, with diverse applications in biomedical research and clinical practice. Iron oxide nanoparticles and gold nanoparticles have been modified to bind to stem cell surface chemical receptors via bioorthogonal copper-free click chemistry, enabling targeted stem cell labeling and efficient internalization for in vivo stem cell tracking[127].

Cell membrane-coated nanoparticles have recently emerged as attractive nanomedicine tools due to their unique properties, including immune evasion, prolonged circulation time, specific molecular recognition, and cell targeting[32,33,128,129]. However, current biomimetic cell membrane coatings have not yet achieved sufficient membrane integrity. Nanoparticles with a high coating degree (> 50%) can directly enter cells, whereas those with a low coating degree (20%–50%) first adhere to the cell surface before synergistic internalization, yet remain effectively engulfed, reflecting the high success rate of cell membrane coating methods, as shown in the **Figure. 6**[130].

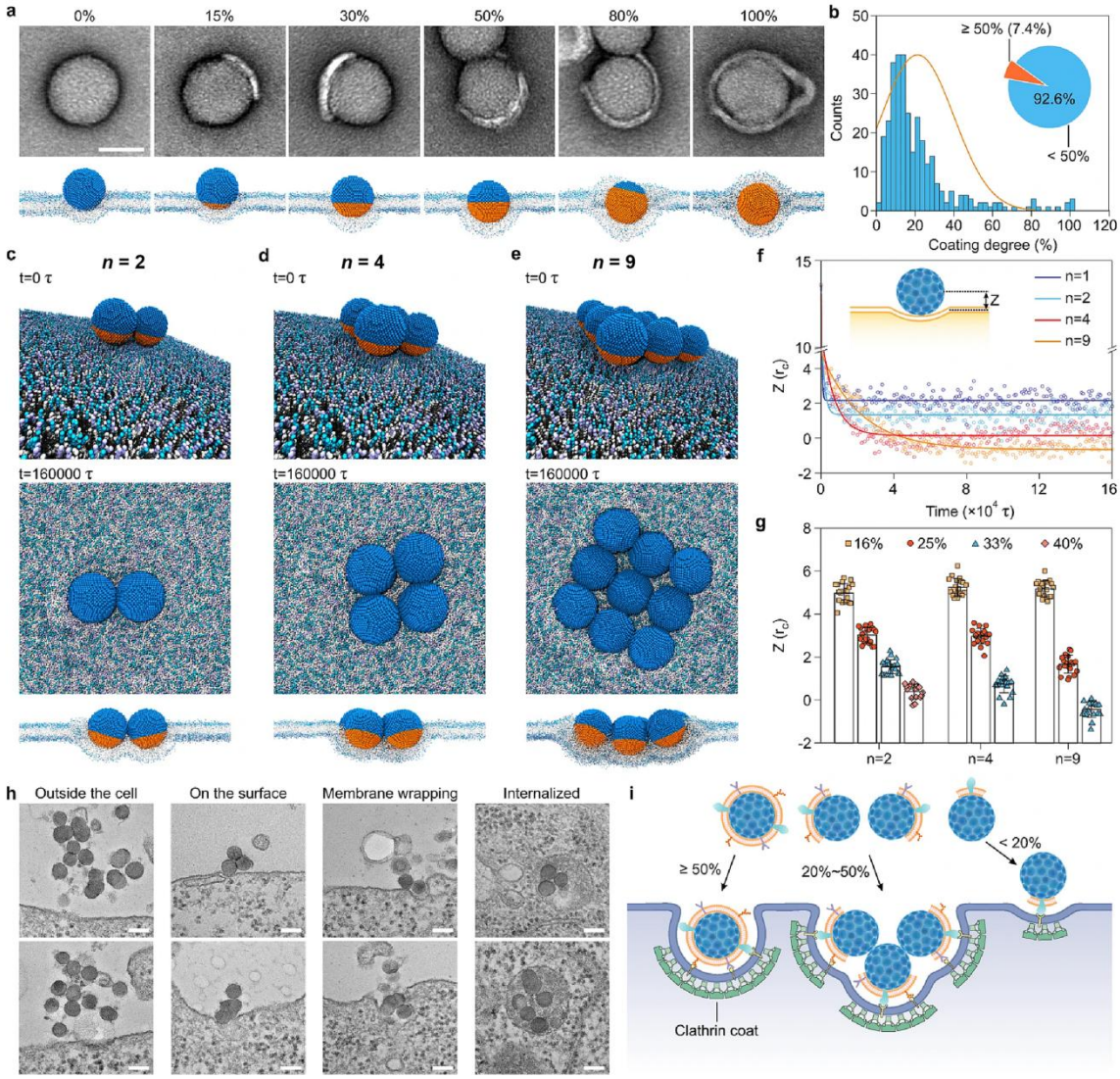


Figure. 6 Cell membrane-coated nanoparticles can directly enter cells. (a) Top: TEM images of SiO_2 nanoparticles with different cell membrane coating degrees (0%, 15%, 30%, 50%, 80%, and 100%). Bottom: the corresponding final dissipative particle dynamics (DPD) simulation snapshots of the wrapping of the cell membrane-coated mesoporous SiO_2 nanoparticles (CM-SiO_2 NPs) by a modeled cell membrane. (b) Cell membrane coating degree distribution of as-prepared CM-SiO_2 NPs. (c–e) Typical DPD simulation snapshots of multiple CM-SiO_2 NPs: aggregation number (n) = 2 (c), 4 (d), and 9 (e). (f) Time evolution of CM-SiO_2 NPs positions along the membrane normal direction. (g) Comparison of positional change of CM-SiO_2 NPs with different aggregated numbers (2, 4, and 9) and coating degrees (16%, 25%, 33%, and 40%). (h) TEM images showing the different states of CM-SiO_2 NPs during receptor-mediated interactions with CT26 cells. (i) Schematic illustration of a possible endocytic entry mechanism for partially coated nanoparticles [130]. Copyright© 2021 Lizhi Liu, Xuan Bai, Maria-Viola Martikainen, Anna Kårlund, Marjut Roponen, Wujun Xu, Guoqing Hu, Ennio Tasciotti, and Vesa-Pekka Lehto.

3.6 Gene Expression

Insertion of exogenous nucleic acids — such as DNA, mRNA, siRNA, microRNA, or antisense oligonucleotides — into cells enables overexpression of specific proteins, thereby modulating stem cell function[131]. Although viral transduction offers high efficiency, its clinical translation is costly and hindered by potential adverse immune responses[132]. In contrast, non-viral vectors can be produced at scale, reduce immunogenicity, and are readily internalized via endocytosis[133].

Currently, lipid nanoparticles represent the most advanced non-viral nucleic acid carriers for delivering mRNA, genome editors, and base editors to stem cells in vivo, and have been utilized in multiple FDA-approved drugs and vaccines, most notably SARS-CoV-2 vaccines[134]. Tello *et al.,* developed hybrid lipid nanoparticles (MSC-Hyb NPs) derived from mesenchymal stem cell extracellular vesicles to deliver *COL1A1* mRNA to tendon stem/progenitor cells. These nanoparticles significantly increased procollagen type I carboxy-terminal peptide (PICP) by approximately two-fold, with 1.96 and 1.92 relative fold change values observed for LNPs and MSC-Hyb NPs, respectively. Its demonstrating their potential for modulating stem cell gene expression in tendon regeneration, as shown in the **Figure. 7**[135]. Lian *et al.,* demonstrated that bone marrow-homing lipid nanoparticles enable in vivo genome editing of disease-related genes. Following intravenous administration to mice, these lipid nanoparticles were internalized by HSCs in the bone marrow and achieved gene editing via CRISPR-Cas9 and base editing. This non-invasive, low-toxicity gene editing strategy holds broad promise for therapeutic genetic drug delivery[136].

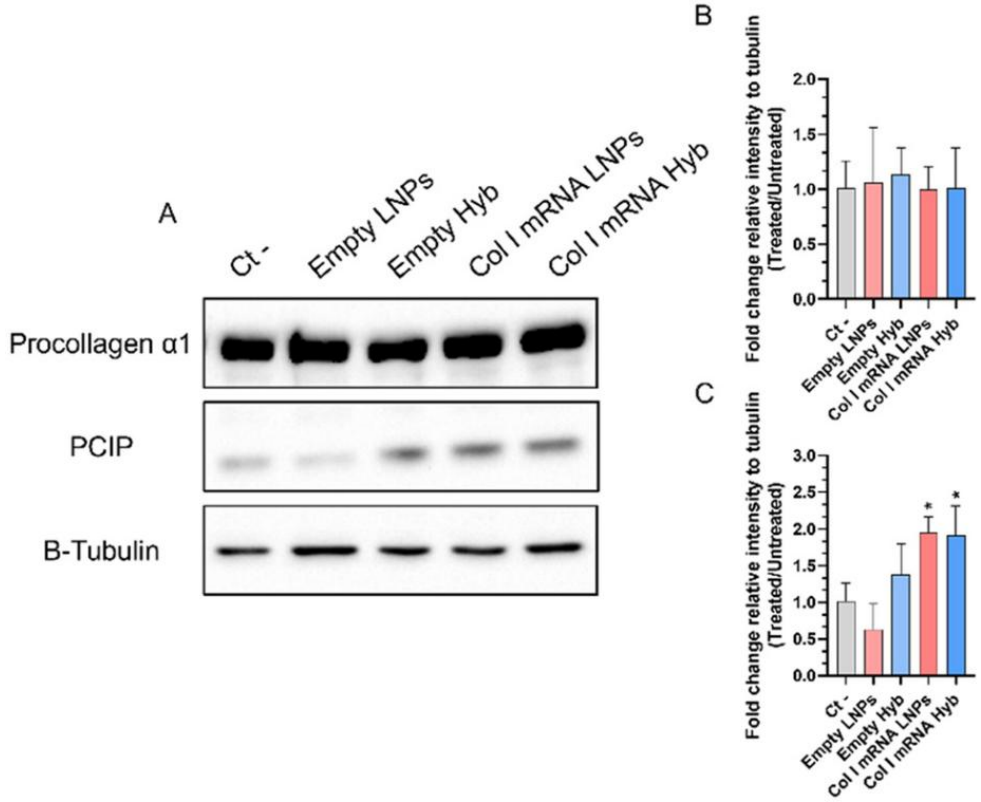


Figure. 7 Lipid nanoparticles modulate *COL1A1* expression in tendon stem cells. (A) Protein expression analysis by western blotting of collagen type I in Tendon stem/progenitor cells (TSPCs) to assess the effect of *COL1A1* mRNA-loaded MSC-derived hybrid (MSC-Hyb) and lipidic nanoparticles (LNPs). (B) Densitometric analysis of procollagen α1 expression normalized to β-tubulin and represented as fold change values relative to the negative control. (C) Densitometric analysis of procollagen type I carboxy-terminal peptide (PICP) expression normalized to β-tubulin and represented as fold change relative to the negative control. (* p-value < 0.05) [135]. Copyright© 2025 Rubén Pareja Tello, Erwin Pavel Lamparelli, Maria Camilla Ciardulli, Jouni Hirvonen, Goncalo Barreto, Nicola Mafulli, Giovanna Della Porta and Hélder A. Santos.

Cationic polymers are commonly used non-viral gene delivery carriers offering greater stability, ease of operation, facile self-assembly with DNA, and lower cost compared to cationic liposomes[137,138]. These polymers typically carry positive charges and interact electrostatically with negatively charged nucleic acids, condensing genetic material into particles hundreds of nanometers in diameter, protecting genes from enzymatic degradation, and mediating cellular entry. For instance, polyethyleneimine (PEI) is one of the most well-known non-viral gene delivery vectors. Researchers have designed a non-viral system using positively charged PEI to chelate negatively charged DNA-loaded PLGA nanoparticles. These modified PLGA nanoparticles interact with negatively charged cell membranes, enter the endoplasmic reticulum, and deliver *SOX5*, *SOX6,* and *SOX9* transgenes to hMSCs, enhancing chondrogenic differentiation[139]. Biodegradable polymer nanoparticles have also been developed to deliver the hVEGF gene to hMSCs and human embryonic stem cell-derived cells (hESdCs). Transgenic hMSCs significantly enhance angiogenesis and limb repair while reducing muscle degeneration and tissue fibrosis[140].

Cationic gene carriers may adsorb negatively charged serum proteins via electrostatic interactions during circulation, increasing nanoparticle size and shifting surface charge from positive to negative. This can hinder binding to negatively charged cell membranes, and adsorbed serum proteins may reduce DNA binding affinity[141,142]. However, magnetic fields can assist cationic gene carriers in resisting serum interference. Consequently, magnetic nanoparticles (MNPs) are widely used as unique transfection reagents in gene therapy research. With the aid of an external magnetic field, large quantities of genes can be concentrated on cell membranes within minutes[143]. For example, Yamoah *et al.,* used MNPs to bind nucleic acids via ionic interactions; nucleic acid-loaded particles were guided by magnetic fields to concentrate on cell membrane surfaces, achieving gene regulation in human induced pluripotent stem cells[144]. The most commonly used Fe_3O_4 and γ-Fe_2O_3 nanoparticles exhibit good superparamagnetism and biocompatibility[145]. Studies have utilized Fe_3O_4 nanoparticles to deliver *NRSF* siRNA and *SHH* siRNA to hADSCs and human amniotic MSCs (hAMSCs), achieving transfection efficiencies up to 80% with interference effects lasting up to 14 days[146]. Thus, superparamagnetic iron oxide nanoparticles (SPIONs) also represent excellent non-viral gene delivery reagents.

In addition, N-(2-hydroxypropyl) trimethylammonium chloride chitosan (HACC), derived from natural chitosan, exhibits strong DNA binding affinity and high DNA protection without cytotoxicity to human cells. These particles possess appropriate nanostructure, average diameter, and DNA release rates, making them an efficient and safe gene delivery tool[147]. Furthermore, combining natural polymers with synthetic polymer-based nanoparticles can enhance compatibility and gene transfer efficiency. For example, chitosan (CS)/tripolyphosphate (TPP)/hyaluronic acid (HA) nanoparticles (CTH nanoparticles) deliver anti-miR-138 to bone marrow MSCs with transfection efficiency nearing 70%, significantly enhance MSC osteogenic activity, and exhibit no toxic side effects[148].

3.7 Inflammation and Immune Response

The acute phase of the inflammatory response represents the earliest immune system reaction to harmful stimuli. Myeloid phagocytes, including dendritic cells and macrophages, play critical roles in this process. Adjacent cells release pro-inflammatory mediators such as interleukin-8 (IL-8) and tumor necrosis factor alpha (TNF-α), leading to activation of neutrophils, fibroblasts, and endothelial cells, as well as the production of other cytokines that can trigger cytokine storms[149]. Persistent or chronic inflammation can severely impair stem cell proliferation and differentiation; thus, mitigating the adverse effects of inflammation on stem cell function is a primary goal in stem cell research. Nanomaterials have opened new directions for inflammation and immune regulation.

The combination of nanoparticles with anti-inflammatory agents offers new avenues for their application in stem cell regenerative medicine. One study utilized aspirin to fabricate carbon nanoparticles for use in BMSCs and evaluated their anti-inflammatory properties. Following 24-hour incubation with 100 μg/mL fluorescent aspirin-based carbon dots, the carbon dots effectively entered BMSCs (approximately 100% uptake). Moreover, qRT-PCR data demonstrated that this novel carbon nanoparticle exhibited superior in vitro anti-inflammatory activity compared to aspirin alone[150].

Additionally, magnesium silicate nanospheres (MSNs) loaded with microRNA-146a-5p have been reported to exert dual osteogenic-promoting and immunomodulatory effects. Beyond synergistically enhancing osteogenic differentiation of human dental pulp stem cells, the delivered miR-146a inhibits the nuclear factor kappa B (NF-κB) pathway by targeting tumor necrosis factor receptor-associated factor 6 (TRAF6), thereby exerting anti-inflammatory effects on lipopolysaccharide-stimulated mouse bone marrow-derived macrophages, as shown in the **Figure. 8**[151].

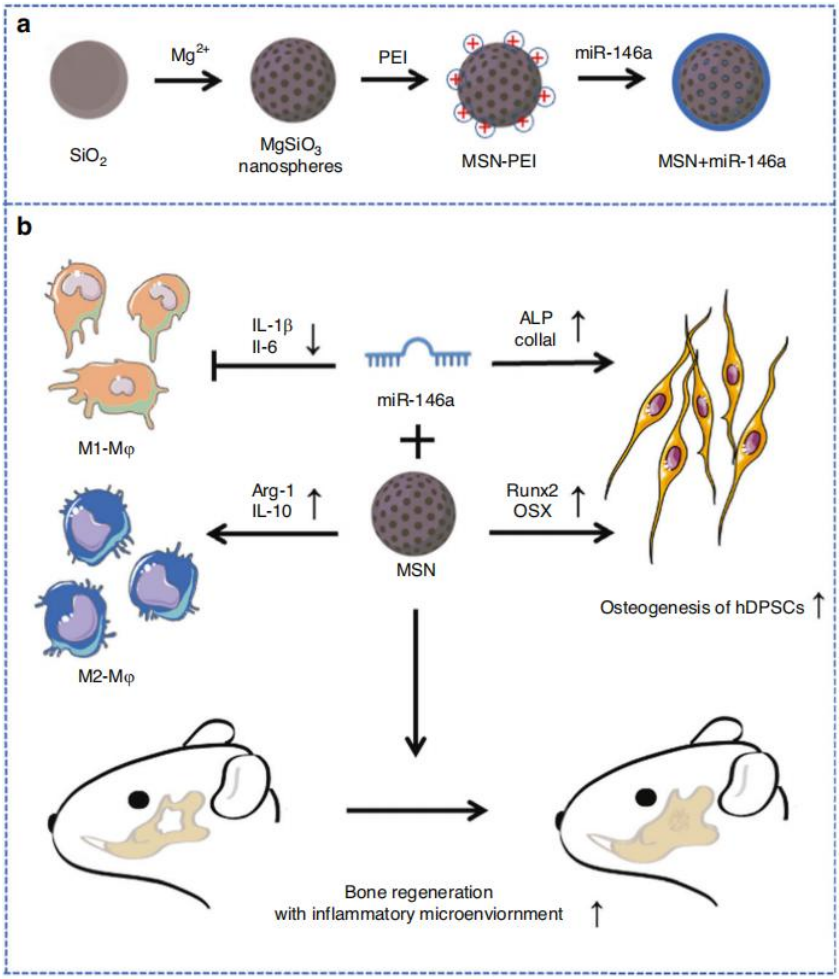


Figure. 8 Nanomaterials regulate the immuno-inflammatory response of stem cells. (a) Magnesium silicate nanospheres (MSNs) were synthesized from SiO2 nanoparticles and modified with polyethyleneimine (PEI), and miR-146a was then loaded via physical absorption and electrostatic attraction. (b) The MSN+miR-146a complex significantly accelerated the osteogenesis of human dental pulp stem cells (hDPSCs), reduced M1-type macrophages, increased M2-type macrophages, and promoted bone regeneration in infected mandibular bone defects in mice[151]. Copyright© 2024 Jiakang Yang, Jing Shuai, Lixuen Siow, Jingyi Lu, Miao Sun, Wenyue An, Mengfei Yu, Baixiang Wang , and Qianming Chen.

A nanoparticle derived from mesenchymal stem cell plasma membranes has been developed, which retains the surface characteristics of MSCs while avoiding regulation by internal cellular mechanisms, thereby endowing the nanoparticle with immunomodulatory and immune evasion capabilities. This nanoparticle has been shown to reduce levels of inflammatory factors such as interleukin-6 (IL-6) and IL-8 in inflammatory cells, acting as an immunomodulatory agent to slow cartilage degeneration[152].

Nanomaterial intervention can influence the activation and function of immune cells — including T cells, B cells, and macrophages — and thereby regulate stem cells. For instance,

calcium alginate nanoparticles serve as a dual-functional therapeutic platform combining bone induction and immune regulation, modulating macrophages to alleviate inflammation and promote bone regeneration. Following cellular uptake, calcium alginate nanoparticles are broken down into calcium ions (Ca^{2+}) and alginic acid within acidic lysosomes. The released Ca^{2+} and alginic acid promote osteogenic and anti-inflammatory microenvironments, respectively. In vitro studies have shown that these nanoparticles enhance osteogenic differentiation of MSCs while mitigating inflammation induced by lipopolysaccharide-activated macrophages[153].

Small extracellular vesicles (DEVs) derived from dendritic cells (DCs) not only inherit the immune regulatory proteins of their parent DCs to activate T cells but also carry photosensitizers that selectively accumulate in tumor cell mitochondria to induce immunogenic cell death. Synergistic photodynamic immunotherapy can trigger robust immune responses and effectively eliminate cancer stem cells[154].

Table 1. Nanomaterials for stem cell function regulation

Regulatory Modes	Biological Functions	Nanomaterials	Application / Mechanism	Reference
Stemness Maintenance	Maintain self-renewal and undifferentiated state	ZnO nanoparticles	Release Zn^{2+} to upregulate *KLF4*, *OCT4*, and *NANOG* expression	[72]
		Ti_2CTX nanosheets (MXene)	High hydrophilicity maintains MSCs stemness	[73]
		PLLA nanofiber membranes	Piezoelectric effect under ultrasound maintains NSCs stemness without exogenous factors	[74]
		Liposome nanoparticles	Encapsulate and sustain release of bioactive factors; antibody-targeted delivery for paracrine control	[71]
		Exosomes (nanovesicles)	Fibronectin-integrin interaction activates FAK pathway; proteomic regulation maintains NSCs quiescence	[76]
Proliferation and Survival	Promote expansion, anti-apoptosis, ROS scavenging	Poly-β-aminoester nanoparticles	Deliver CXCR4 plasmid to enhance ADSC engraftment and survival	[79]
		Mn-Co_3O_4 nanoparticles	Increased Co^{2+}/Co^{3+} ratio enhances ROS scavenging, protecting hMSCs	[80]
		Cerium oxide nanomaterials (nanorods, nanowires)	Size-dependent ROS scavenging (intracellular/extracellular); short forms better protect proliferation	[81]
		AuNPs (60 nm)	Activate Wnt/β-catenin pathway to promote periodontal ligament stem cell proliferation	[82]
Differentiation	Induce osteogenic, neural, adipogenic differentiation	AuNPs (13 nm, 45 nm)	Size-dependent autophagy regulation; 45 nm most effective for osteogenesis	[102]
		AuNPs (spheres vs. rods)	Sphere-70 nm and rod-70 nm promote ALP/calcium deposition; rod-40 nm inhibits osteogenesis	[103]
		Functionalized silica nanoparticles	Surface charge (phosphate/sulfonate groups) regulates osteogenic gene expression	[104]
		Graphene quantum dots (GQD^-)	Negative charge activates BMP/Smad pathway to enhance osteogenesis	[105]
		Magnetic nanoparticles (MNPs)	Magnetic force controls cell-matrix tension, activating MAPK and YAP/RUNX2	[106]
		Upconversion nanoparticles (UCNPs)	NIR-responsive release of differentiation factors for guided NSCs differentiation	[107]
Adhesion, Migration, and Homing	Cell anchoring, directional movement, targeted homing	Poly(L-lysine) (PLL) nanosheets	Molecular weight-dependent interfacial toughness regulates MSC adhesion and spreading	[109]
		Superparamagnetic iron oxide nanoparticles	Conjugated with adhesive ligands; magnetic field controls integrin-mediated adhesion	[115]
		Clay nanoparticles (montmorillonite) doped hydrogels	Improve PVA adhesion properties to enhance stem cell attachment	[116]
		Hydroxyapatite (HA) nanoparticles (nanosheets)	Nanosheet structure regulates actin cytoskeleton to promote adhesion	[117]
		PEGylated AuNPs	Internalized by MSCs; upregulate actin/tubulin expression to increase migration	[120]
		Alendronate-modified liposome nanoparticles	Bone-targeted SDF-1 delivery creates chemokine gradient to induce stem cell homing	[122]

Table 1. Nanomaterials for stem cell function regulation (continued)

Regulatory Modes	Biological Functions	Nanomaterials	Application / Mechanism	Reference
Internalization and Absorption	Cellular uptake efficiency and pathways	Spherical vs. ellipsoidal polymer nanoparticles	Ellipsoids show higher adsorption but lower uptake; aspect ratio negatively correlates with uptake	[124]
		Soft vs. hard nanoparticles	Soft particles evade phagocytosis with longer circulation; hard particles favor intracellular uptake	[125, 126]
		Surface-modified iron oxide/gold nanoparticles	Bioorthogonal click chemistry enables receptor-specific binding and efficient internalization	[128]
		Cell membrane-coated nanoparticles	High coating (> 50%) enables direct entry; low coating (20%–50%) requires synergistic entry; both confer immune evasion	[130]
Gene Expression	Exogenous gene delivery and editing	Lipid nanoparticles (LNPs)	Deliver mRNA/Cas9 for in vivo HSC gene editing (base editing, CRISPR-Cas9)	[134]
			Deliver *COL1A1* mRNA to tendon stem/progenitor cells	[135]
		PEI-modified PLGA nanoparticles	Deliver *SOX5/6/9* genes to enhance MSC chondrogenic differentiation	[139]
		Magnetic nanoparticles (Fe_3O_4, SPION)	Magnetic field-assisted transfection; deliver siRNA (*NRSF, SHH*) with up to 80% efficiency	[145, 146]
		N-2-hydroxypropyl trimethylammonium chloride chitosan (HACC)	High DNA binding affinity; low cytotoxicity for safe gene delivery	[147]
		Chitosan/TPP/hyaluronic acid (CTH) nanoparticles	Deliver anti-miR-138 with ~70% transfection efficiency; enhance MSC osteogenesis	[148]
Inflammation and Immune Response	Anti-inflammation, immunomodulation	Aspirin-based carbon nanoparticles	Efficiently enter BMSCs (~100%); superior anti-inflammatory activity compared to free aspirin	[150]
		miR-146a-loaded magnesium silicate nanospheres	Inhibit TRAF6/NF-κB pathway; dual osteogenic promotion and anti-inflammatory effects	[151]
		MSCs membrane-coated nanoparticles	Retain MSC surface properties; reduce IL-6/IL-8 levels; immunomodulatory for cartilage protection	[152]
		Calcium nervonate nanoparticles	Lysosomal release of Ca^{2+} (osteogenic) and nervonic acid (anti-inflammatory); bidirectional immunomodulation	[153]
		Dendritic cell-derived small extracellular vesicles (DEVs)	Carry immunoregulatory proteins and photosensitizers; synergize with photodynamic immunotherapy to kill cancer stem cells	[154]

NOTE: *KLF4*: Krüppel-like factor 4; *OCT4*: Octamer-binding transcription factor 4; *NANOG*: *Nanog* homeobox; MSCS: Mesenchymal Stromal Cells; NSCs: Neural Stem Cells; ROS: Reactive Oxygen Species; *CXCR4*: C-X-C chemokine receptor type 4; ADSC: Adipose-derived stem cells; BMP: Bone morphogenetic protein; MAPK: Mitogen-activated protein kinase; YAP: Yes-associated protein; RUNX2: Runt-related transcription factor 2; PVA: Polyvinyl alcohol; HSC: Hematopoietic stem cells; *COL1A1*: Collagen type I alpha 1 chain; PLGA: Poly(lactic-co-glycolic acid); *NRSF*: Neuron-restrictive silencer factor; *SHH*: Sonic hedgehog; BMSCs: Bone marrow mesenchymal stem cells.

4. The Regulatory Mechanisms of Nanomaterials on Stem Cells

4.1 Wnt/β-Catenin Signaling Transduction

The Wnt signaling pathway is vital for embryonic development, tissue homeostasis, and disease pathogenesis[155,156]. By binding to specific receptors, Wnt ligands regulate cell fate, proliferation, and differentiation[157]. In the most well-studied Wnt/β-catenin pathway, Wnt ligands bind Frizzled receptors and LRP5/6 co-receptors[158,159]. This cascade regulates β-catenin stability and transcriptional activity[160], driving cell fate decisions and progenitor self-renewal.

This pathway is particularly critical in stem cells[161,162], governing their proliferation, self-renewal, and pluripotency[163-165], including that of MSCs[166] and ESCs[167]. Modulating this signaling enables precise control over stem cell fate, enhancing its applications in regenerative medicine.

The mechanism of the Wnt/β-catenin signaling pathway involves several steps and molecules. In the absence of Wnt signaling, *β-catenin*, which functions as both a cell adhesion protein and a transcriptional co-regulator, is phosphorylated by *CK1* and the *APC/Axin/GSK-3β* complex[168,169]. This phosphorylation facilitates β-catenin's ubiquitination and proteasomal degradation via the β-TrCP/Skp pathway[170]. When Wnt ligands are present, they bind to Frizzled receptors and LRP5/6 co-receptors, forming a complex that activates *Dishevelled* (*Dvl*)[171-173]. This activation leads to the phosphorylation, polyubiquitination, and aggregation of *Dvl*. Consequently, stable β-catenin accumulates in the nucleus, where it is transported with the aid of *Rac1* and other factors[174]. Once in the nucleus, β-catenin interacts with TCF/LEF transcription factors, displacing co-repressors and recruiting additional co-activators to *Wnt* target

genes[175,176]. Furthermore, β-catenin collaborates with other transcription factors to regulate the expression of specific target genes[177-179]. This entire signaling cascade is schematically illustrated in the **Figure. 9.**

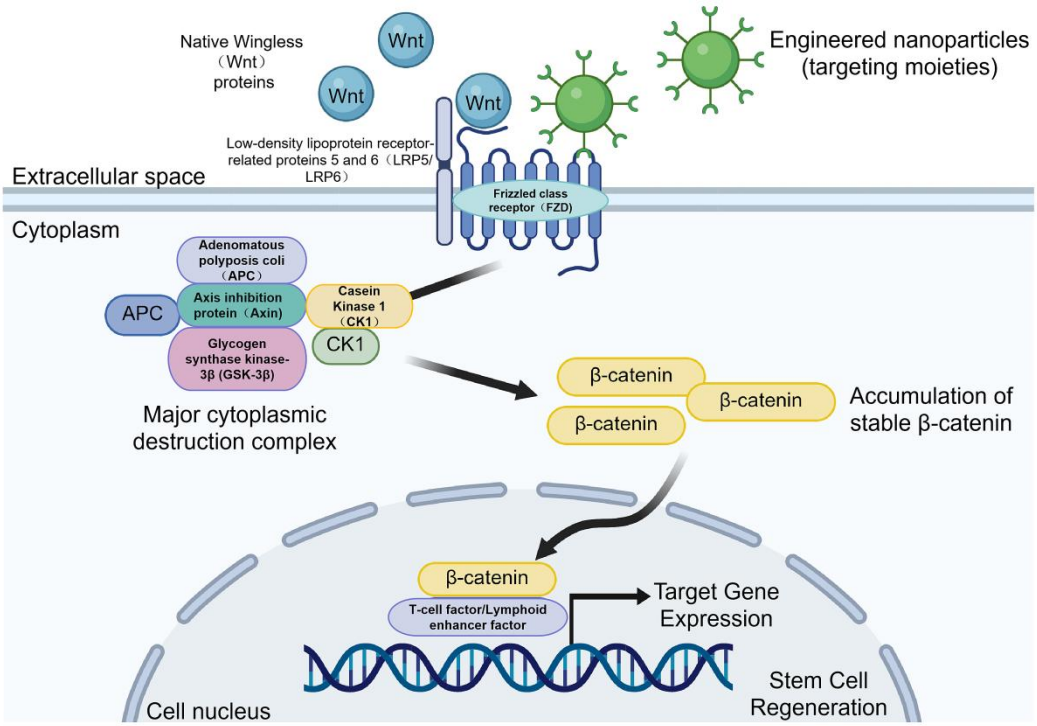


Figure. 9 Schematic of the nanomaterial-modulated Wnt/β-catenin signaling pathway in stem cells. Created by the author using Microsoft PowerPoint.

Stem cells are crucial for development, tissue homeostasis, and repair. The Wnt/β-catenin pathway centrally regulates their differentiation and function, particularly in osteoblasts and neural stem cells[180-183]. Consequently, NPs have emerged as powerful biomedical tools to modulate this pathway, steering stem cell behavior through diverse mechanisms.

Through surface modifications, NPs can directly target membrane receptors. For instance, immobilizing Wnt peptides on MNPs to target Frizzled-2 effectively activates the canonical Wnt and TCF/LEF signaling cascade, demonstrating precise pathway modulation[184,185].

Various nanomaterials promote osteogenic differentiation by activating this pathway. Chitosan-conjugated AuNPs significantly enhance calcium deposition and osteogenic marker expression in adipose-derived stem cells (ADSCs)[186]. Similarly, cerium oxide (CeO_2) NPs facilitate β-catenin nuclear translocation by upregulating the Simplet protein. Furthermore, bFGF-loaded mesoporous silica nanoparticles (MSNs) and iron oxide nanoparticles (IONP-CM) effectively induce osteogenesis and bone formation[187]. NPs can also be integrated into complex biomaterials to address pathological microenvironments. An antioxidant chitosan/alginate hydrogel loaded with selenium NPs (SeNPs/CMC/Alg) activates Wnt/β-catenin to promote BMSC osteogenesis while scavenging excess ROS[188]. This system demonstrated remarkable therapeutic efficacy for necrotic femoral heads under oxidative stress.

Notably, nanomaterial-mediated regulation includes pathway inhibition. Titanium (Ti) NPs with specific topographies promote BMSC osteogenesis by inhibiting integrin-linked kinase (ILK) or Wnt/β-catenin signaling, optimizing cell attachment and osseointegration[189].

In summary, due to their high surface area and tunable surface chemistry, NPs offer irreplaceable advantages for spatiotemporally modulating stem cell signaling. They enable precise pathway activation or inhibition and serve as versatile delivery vectors, making stem cell-based tissue regeneration significantly more controllable and efficient.

4.2 TGF-β Signaling Transduction

The highly conserved transforming growth factor-beta (TGF-β) signaling pathway plays a pivotal role in regulating cell proliferation, differentiation, and development[190-192]. It is crucial for maintaining tissue homeostasis, mediating damage repair, and modulating overall cell behavior[193]. In stem cell biology, TGF-β signaling meticulously governs cell fate by regulating cell cycle genes to preserve self-renewal and multipotency, while also guiding specific lineage differentiation for tissue regeneration. This dual regulation is vital for their physiological functions and therapeutic applications.

In the initial step of TGF-β signal transduction, TGF-β ligands bind to a heteromeric complex of type II and type I receptors, leading to a conformational change in TGF-βRII, which then forms a heterotetrameric complex with type I receptors (TGF-βRI). The type II receptor is a serine/threonine kinase with intrinsic kinase activity, which phosphorylates and activates the type I receptor upon ligand binding[194-196]. The activated TGF-βRI receptor continues to phosphorylate receptor-regulated SMAD proteins (R-SMADs), primarily SMAD2 and SMAD3. Once phosphorylated at the C-terminal, R-SMADs bind to the common-SMAD (Co-SMAD), SMAD4, forming an R-SMAD/SMAD4 complex. This trimeric complex translocates to the nucleus, where it associates with high-affinity DNA-binding transcription factors (TF) and chromatin remodeling proteins (CR), thereby regulating the transcription of target genes[197-203], as schematically illustrated in the **Figure. 10**.

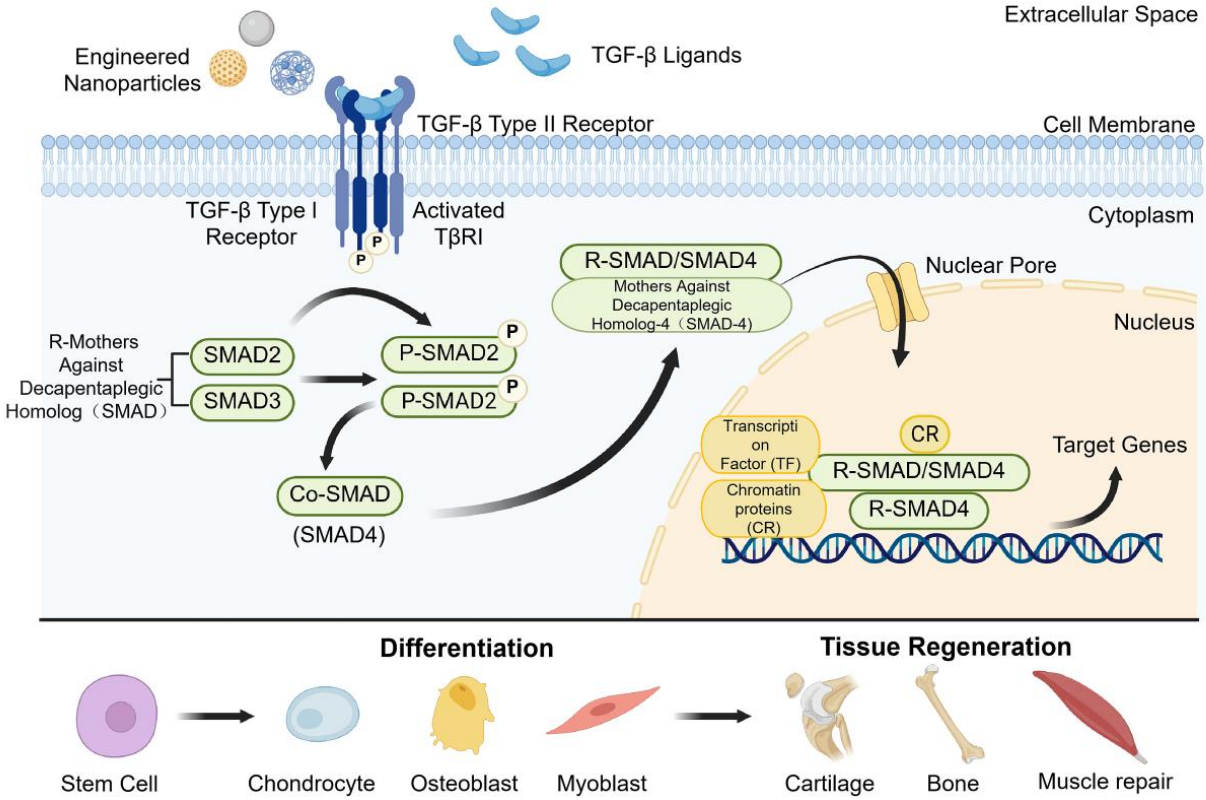


Figure. 10 Schematic illustration of the nanomaterial-modulated TGF-β signaling pathway in stem cells for tissue regeneration. Created by the author using Microsoft PowerPoint.

The TGF-β pathway is fundamentally essential for maintaining tissue homeostasis, governing stem cell differentiation, and orchestrating repair. Nanomaterials can precisely modulate this critical cascade to exert stringent control over stem cell proliferation, directed differentiation, and self-renewal. Consequently, this targeted nanotherapeutic regulation significantly advances the efficacy of stem cell-mediated tissue regeneration and functional recovery[204].

Bone Regeneration: Nanoscale biomaterials provide crucial structural and biochemical cues for osteogenesis. For example, boron-encapsulated nanoscale hydroxyapatite composites significantly upregulate ALP activity and TGF-β-related osteogenic genes in MSCs[205]. Furthermore, nanoceria (nCe) scaffolds amplify osteogenic potential through synergistic integrin-mediated mechanotransduction and TGF-β co-signaling, substantially enhancing bone regenerative therapies[206].

Cartilage and Periodontal Tissue Repair: Sustained, localized morphogen delivery is paramount for soft tissue regeneration. Mineralized extracellular matrix/dental pulp stem cell microspheres (MMCMs) facilitate functional periodontal tissue regeneration by continuously releasing TGF-β1 to activate the TGF-β1/Smad3 cascade [207].

Tendon Regeneration: Tendon engineering requires specific structural and biomechanical mimicry. Biomimetic bimodal micro-nanofiber scaffolds replicate the hierarchical architecture of native tendons, enhancing the biomechanical responsiveness of tendon stem/progenitor cells (TSPCs) to activate the TGF-β/Smad2/3 pathway and promote tenogenesis. Furthermore, integrating functionalized MNPs with magnetically responsive scaffolds [208]. enables remote, spatiotemporal actuation of TSPCs under external magnetic fields. This precision control vigorously upregulates tendon-specific gene expression via TGF-β/Smad2/3 activation, introducing a high degree of precision into tendon repair [209].

4.3 Notch Signaling Transduction

The highly conserved Notch signaling pathway governs cell fate determination during development and maintains adult tissue homeostasis. In stem cell biology, it profoundly influences proliferation, differentiation, and self-renewal, driving the regeneration of nervous, cardiac, immune, and endocrine tissues. Consequently, Notch signaling remains a core focus in regenerative medicine[210-212].

Operating via direct cell-to-cell contact, mammalian Notch signaling involves four receptors (Notch1-4) and multiple ligands, including Jagged (JAG1/2) and Delta-like proteins (DLL1/3/4)[213-215]. These receptors are single-pass transmembrane heterodimers featuring extracellular epidermal growth factor-like repeats[216]. Prior to membrane presentation, they undergo cleavage and glycosylation in the endoplasmic reticulum and Golgi apparatus to maintain a stable heterodimeric state.

Upon ligand binding from an adjacent cell, the Notch receptor undergoes sequential cleavage[217-219]. First, the Notch extracellular domain (NECD) is cleaved by an ADAM metalloprotease (TACE)[220]. Subsequently, γ-secretase cleaves the transmembrane domain, releasing the Notch intracellular domain (NICD)[221]. The NICD then translocates to the nucleus, where it binds to the CSL transcription factor complex, leading to the activation of downstream target genes such as *MYC*, p21, and members of the HES family. The activation of these genes is crucial for determining cell fate, self-renewal, and differentiation processes[222,223], as depicted in the **Figure. 11**.

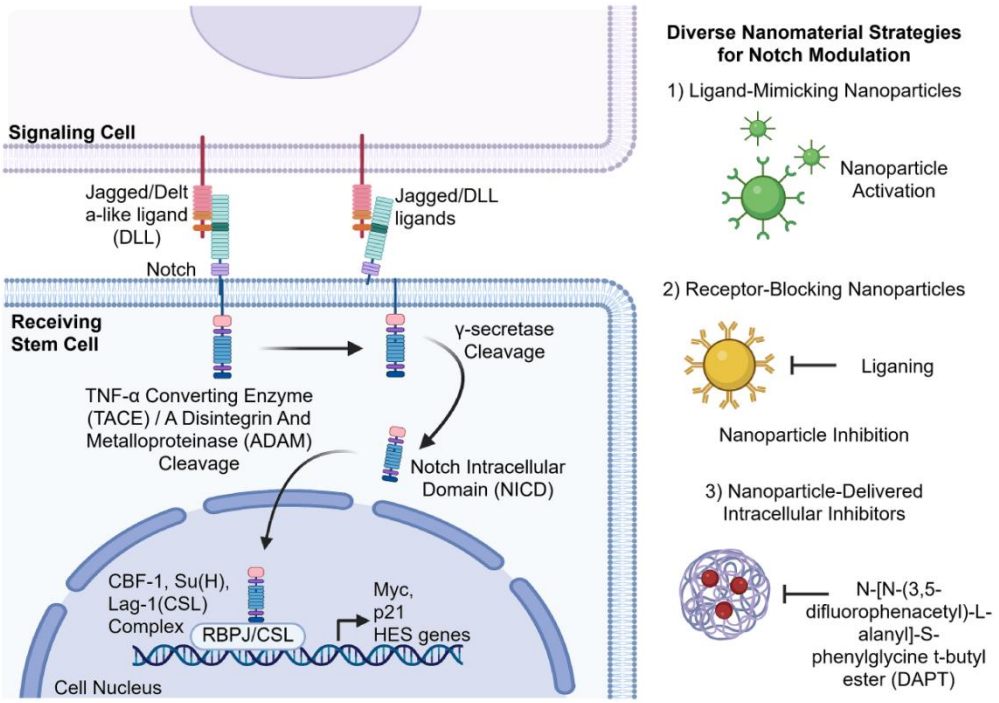


Figure. 11 Schematic illustration of the Notch signaling pathway modulated by nanomaterials in stem cells. Created by the author using Microsoft PowerPoint.

The Notch signaling pathway fundamentally regulates stem cell fate and tissue regeneration. Consequently, nanomaterials and surface engineering have emerged as versatile platforms to modulate this cascade, enhancing stem cell differentiation and regenerative capacity across various tissues, including muscle, bone, and cornea.

Nanocarriers offer precise spatiotemporal control over Notch signaling, functioning either as delivery vehicles or intrinsic cues. For instance, polymer-engineered mesoporous silica nanoparticles (MSNs) enable the targeted, delayed release of γ-secretase inhibitors. This controlled blockade effectively drives myogenic differentiation without disrupting broader physiological homeostasis[224]. Conversely, tetrahedral DNA nanostructures (TDNs) act as active signaling agents rather than mere carriers. TDNs robustly activate Notch signaling to enhance the osteogenic and odontogenic differentiation of dental pulp stem cells, offering innovative DNA-based molecular strategies for skeletal repair[225].

Beyond targeted delivery, nanomaterial composition and scaffold anisotropy regulate Notch-mediated osteogenesis. Multi-walled carbon nanotubes (MCNTs) induce osteogenic differentiation in adipose-derived mesenchymal stem cells more effectively than nano-hydroxyapatite by activating Notch signaling[226]. Additionally, a chitosan/alginate hydrogel co-loaded with parathyroid hormone (PTH) (1–34) and nano-hydroxyapatite promoted rBMSC osteogenesis via the Notch pathway, significantly enhancing in vivo cranial bone regeneration[227].

In corneal repair, micro- and nanoscale topographies on silk films alter human corneal limbal epithelial cell differentiation, with transcriptomic analyses implicating Notch signaling[228]. Independent studies confirm Notch as a key regulator here: Jagged1-mediated Notch activation reduces stem/progenitor markers and epithelial stratification, whereas Notch inhibition maintains the undifferentiated state of limbal stem cells[229,230]. Together, these biophysical cues likely guide corneal stem cell fate through Notch-linked mechanotransduction.

Finally, for cartilage repair, Wharton's jelly mesenchymal stem cell-derived small extracellular vesicles (WJMSC-sEVs) promoted chondrogenesis in osteoarthritis models, with RNA-seq confirming Notch pathway involvement in this regenerative response[231].

5. Prospects for the Application of Nanomaterials

5.1 Microfluidic Technology Improves Material Preparation Control and Stem Cell Applications

One of the most challenging areas of nanotechnology is the production of nanomaterials for biomedical applications. Traditional batch reactors often suffer from poor control of reaction kinetics, low reproducibility, and uneven particle size distribution during mass production, making it difficult to achieve desired nanomaterial characteristics[232]. Microfluidic technology enables precise control over each step of nanomaterial formation.

Microfluidic devices operate using small fluid volumes through channels ranging from tens to hundreds of micrometers[233]. Due to their high specific surface area, reagents undergo rapid heating and cooling, maintaining isothermal conditions[234]. Additionally, microfluidic reactions are faster than traditional batch reactors, consume less reagent, reduce synthesis costs, and enhance equipment safety for transport and storage. Microfluidic technology allows real-time monitoring of reaction spatial and temporal evolution, enabling continuous tracking of reaction parameters and generated nanoparticles. With programmable devices and real-time monitoring, material preparation automation can be achieved[235]. Nanoparticles synthesized via microfluidic technology exhibit superior biological stability and performance

compared to those produced by traditional methods, further enhancing their biomedical applications.

Beyond material preparation, microfluidic technology enables precise control and efficient operation of stem cell culture. Controllable and reproducible droplet sequences can be generated through microfluidic devices to simulate stem cell niches, creating ideal three-dimensional culture environments for cell separation, cultivation, and cell–cell interactions[236]. Encapsulating stem cells in droplets allows single-cell screening or quantification, analysis of intracellular and extracellular protein expression, and facilitates comprehensive understanding of cell–biomaterial interaction mechanisms.

5.2 Evaluation of Stem Cells Induced by Biomaterials Using Artificial Intelligence

Traditional techniques for evaluating the impact of nanomaterials on stem cell differentiation — such as microscopic observation with various staining methods, flow cytometry, PCR, and Western blotting to identify lineage-specific biomarkers have limitations. Additionally, analyzing data from different materials or batches requires cumbersome standardization, making the process time-consuming, labor-intensive, and uneconomical, thereby hindering research progress in this field[237]. Therefore, more effective, accurate, and convenient methods are urgently needed to support cross-laboratory, cross-material, and batch-independent functional evaluation comparisons of biomaterials.

The application of artificial intelligence in biomedicine offers a new direction. Multiple studies suggest that machine learning can be used for accurate predictions; for example, recent research has shown that machine learning can identify morphological changes from microscopic images to predict the development and lineage differentiation levels of HSCs before the onset of developmental processes[238,239]. The potential for further application of machine learning in biomaterials research has been emphasized, with big data serving as the foundation for successful machine learning models. Machine learning can not only identify physiological differences between cell types but also construct models by learning from genome-wide gene expression data of multiple differentiated cells to determine cellular functional changes induced by biomaterials based on overall gene expression patterns[240,241].

Regarding nanomaterial safety, the integration of advanced analytical and computational tools can quantitatively provide information on molecular changes within biological systems under toxic exposure, revealing how biological networks are affected by toxic insults[242]. With the application of machine learning and deep learning methods, large volumes of complex biomedical data can be processed and analyzed[243]. Machine learning enables quantitative prediction of nanomaterial cytotoxicity, and bioinformatics approaches allow simultaneous development of experimental and computational methods with good coordination between data collection and computational modeling[244]. This facilitates the identification of novel interaction patterns between nanomaterials and stem cells, the prediction of material biological effects, and the discovery of key factors influencing stem cell fate.

Furthermore, the integration of advanced omics technologies particularly single-cell RNA sequencing (scRNA-seq) and spatial transcriptomics (ST) represents a transformative frontier for evaluating stem cell-biomaterial interactions. While traditional bulk transcriptomics obscures cellular heterogeneity, scRNA-seq resolves distinct subpopulations, and ST maps these gene expression profiles while preserving native 3D histological architecture. This spatial context is vital for accurately evaluating how nanomaterials locally orchestrate stem cell migration characteristics, stemness maintenance, and specific differentiation capacities within complex tissue microenvironments. When coupled with artificial intelligence and deep learning, these massive, multidimensional omics datasets allow researchers to decipher complex spatiotemporal signaling networks, offering unprecedented precision in predicting stem cell fate and optimizing the rational design of nanomaterials[245].

5.3 Synergistic Modulation of Multi-Signal Pathways

Given its indispensable role in cell growth, lineage-specific differentiation, and immune modulation, the TGF-β pathway remains a paramount target for advanced nanomaterial design. A primary frontier is developing stimulus-responsive nanocarriers for the precise spatiotemporal delivery of TGF-β modulators. For instance, integrating magnetic nanoparticles (MNPs) and photoresponsive nanoplatforms enables the externally triggered, on-demand release of TGF-β signals, maximizing therapeutic efficacy while mitigating off-target effects.

Furthermore, authentic tissue regeneration relies on multiple molecular cascades. Consequently, next-generation nanotherapeutics must evolve from mono-target strategies to integrated, multi-signal systems. Synergistically modulating TGF-β alongside the Wnt/β-catenin and Notch pathways allows engineered biomaterials to closely mimic the dynamic physiological milieu. This combinatorial regulation will significantly enhance stem cell therapies, which are vital for the structural and functional regeneration of complex organs like the skin, liver, and lungs.

Overall, nanomaterial-directed stem cell regulation is becoming increasingly refined and intelligent. Converging materials science, molecular biology, and nanotechnology enables the development of smart nanotools to autonomously orchestrate Notch, Wnt, and TGF-β networks. Ultimately, these platforms will catalyze breakthroughs in tissue engineering and regenerative medicine, providing unprecedented therapeutic paradigms for complex and refractory diseases.

5.4 Stem Cell Rejuvenation and Longevity

While current research heavily emphasizes the physicochemical design of nanomaterials, the ultimate frontier of regenerative medicine lies in addressing pathological aging and promoting longevity. Aging is universally characterized by stem cell exhaustion, cellular senescence, and the progressive deterioration of the tissue microenvironment. Future nanomaterial strategies must shift from merely repairing acute injuries to actively rejuvenating aged tissues. For instance, functionalized nanocarriers can be engineered to deliver senolytic agents that selectively clear senescent cells, or to scavenge senescence-associated reactive oxygen species (ROS) to restore a youthful stem cell niche. Furthermore, nanomaterials hold immense potential in driving metabolic reprogramming such as mediating the reversal of age-associated white adipose tissue accumulation to restore metabolic homeostasis. By directly intervening in the fundamental mechanisms of aging, engineered nanomaterials will play a pivotal role in extending the functional healthspan of tissues and realizing the clinical goals of longevity.

6. Conclusion

Nanomaterials, owing to their unique physicochemical

properties, such as high specific surface area, good biocompatibility, controlled release capability, targeting potential, and distinct optical and magnetic characteristics have demonstrated immense potential in stem cell research. These properties enable nanomaterials to serve not only as efficient carriers for drugs, genes, and bioactive factors but also as active modulators of stem cell behavior. By providing an optimized microenvironment, nanomaterials can effectively regulate key stem cell functions, including stemness maintenance, proliferation and survival, directed differentiation, adhesion, migration and homing, internalization, gene expression, and immune responses.

Notably, nanomaterials exert their regulatory effects through precise modulation of critical signaling pathways, such as Wnt/β-catenin, TGF-β, and Notch, which are essential for stem cell fate determination, self-renewal, and tissue regeneration. Through surface functionalization, controlled release mechanisms, and stimuli-responsive designs, nanomaterials enable spatiotemporally controlled manipulation of these pathways, offering unprecedented precision in steering stem cell behavior for therapeutic purposes.

Looking forward, the integration of emerging technologies such as microfluidic platforms (for precise synthesis and scalable production) and artificial intelligence (for high-throughput analysis and predictive modeling) will be instrumental in overcoming current limitations. These approaches will facilitate the rational design of next-generation nanomaterials with enhanced functionality, safety, and clinical translatability. Ultimately, the continued convergence of nanotechnology, stem cell biology, and advanced manufacturing holds great promise for the development of innovative regenerative medicine strategies and the successful clinical translation of nanomaterial-enhanced stem cell therapies.

Author Contributions

Concptualization: Ping Zhang, Huan Zhou, Lei Yang; Investigation, Writing Original Draft and Visualization: Xuetong Wang, Yiming Sun; Writing – Review & Editing, Supervision and Funding Acquisition: Ping Zhang, Huan Zhou, Lei Yang.

Informed Consent Statement

The authors declare no competing financial interests.

Conflicts of Interest

The authors declare no conflict of interest.

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