

Nanoparticle-labeled stem cells: a novel therapeutic vehicle

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Abstract: Nanotechnology has been described as a general purpose technology. It has already generated a range of inventions and innovations. Development of nanotechnology will provide clinical medicine with a range of new diagnostic and therapeutic opportunities such as medical imaging, medical diagnosis, drug delivery, and cancer detection and management. Nanoparticles such as manganese, polystyrene, silica, titanium oxide, gold, silver, carbon, quantum dots, and iron oxide have received enormous attention in the creation of new types of analytical tools for biotechnology and life sciences. Labeling of stem cells with nanoparticles overcame the problems in homing and fixing stem cells to their desired site and guiding extension of stem cells to specific directions. Although the biologic effects of some nanoparticles have already been assessed, information on toxicity and possible mechanisms of various particle types remains inadequate. The aim of this review is to give an overview of the mechanisms of internalization and distribution of nanoparticles inside stem cells, as well as the influence of different types of nanoparticles on stem cell viability, proliferation, differentiation, and cytotoxicity, and to assess the role of nanoparticles in tracking the fate of stem cells used in tissue regeneration.

Keywords: nanoparticles, stem cells, uptake, differentiation, cytotoxicity, tracking

Nanotechnology

Nanotechnology is defined as the technology that deals with objects of nanometer (10^{-9} meter) size. It refers to the research and development which leads to the controlled manipulation and study of structures and devices in the range of 1–100 nanometers.^{1,2} It involves imaging, measuring, modeling, and manipulating matter at this measurement size.³ In addition, nanotechnology entails the use of atomic, molecular, and submolecular structures as core building blocks to create new products and devices. The resulting products and devices are collectively called nanomaterials. Each element is known as a nanoparticle.⁴

Nanoparticles can have different shapes and compositions. Their very small size imparts physical and chemical properties, particularly their high surface to volume ratio, surface tailorability, improved solubility, multifunctionality, high electrical and heat conductivity, and improved surface catalytic activity that are very different to those of the same material in the bulk form.⁵ These nanoparticles can be categorized into carbon-based materials, such as fullerenes and carbon nanotubes, and inorganic nanoparticles including the ones based on metal oxides (eg, zinc oxide, iron oxide, titanium dioxide, and cerium oxide), metals (gold, silver, and iron) and quantum dots (cadmium sulfide and cadmium selenide).

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Mixtures of different phases are also manufactured. In addition, these nanomaterials also present different and interesting morphologies such as spheres, tubes, rods, and prisms. Nanotechnology includes the integration of these nanoscale structures into larger material components and systems, keeping the control and construction of new and improved materials at the nanoscale.⁶

Nanotechnology has been described as a general purpose technology. It has already generated a range of inventions and innovations. The scientific knowledge base of nanotechnology is considered to be very interdisciplinary and multidisciplinary, combining various subfields of physics and chemistry in its extension of material sciences.³ Manufactured nanoparticles are currently used to develop products in many fields including communication, engineering, electronics, optics, energy, computer science, biology, pharmaceuticals, chemistry, cosmetics, the food industry, environmental analysis and remediation, catalysis, and material sciences.⁶⁻⁸

Nanomedicine

One of the major developments in nanotechnology and nanoscience studies is the production and application of nanoparticles in medical sciences, which is referred as nanomedicine. It portends a potentially endless range of applications from biomedical imaging and drug delivery to therapeutics and tissue regeneration, as well as the development of new medical products.⁹

Nanotechnology uses engineered materials or devices with the smallest functional organization that are able to interact with biologic systems at a molecular level. Thus, they may stimulate, respond to, and interact with target cells and tissues in order to induce desired physiologic responses while minimizing undesirable side effects. Furthermore, nanomedicine may offer ways to manipulate complex biologic systems with greater selectivity and timing than conventional pharmacologic approaches.¹⁰ The chemistry and physics of materials change more notably with size at the sub-100 nm length scales. Transcription and translation within a cellular organism occurs within the subnanometer range, and with the advent of techniques and technologies available to create materials small enough to interact selectively with biologic molecules such as nucleic acids and proteins, new opportunities to study cellular level activities are being made available.¹¹ Nanometer-sized particles are in the same range of dimension as antibodies, membrane receptors, nucleic acids, and proteins, among other biomolecules. These biomimetic features, together with their high surface to volume ratio

and the possibility of modulating their properties, make nanoparticles powerful tools for imaging, diagnosis, and therapy.⁷ Nanomedicine includes nanoparticles that act as biologic mimetics (eg, functionalized carbon nanotubes), “nanomachines” (eg, those made from interchangeable DNA parts and DNA scaffolds such as the octahedron and stick cube), nanofibers, and polymeric nanoconstructs as biomaterials (eg, molecular self-assembly and nanofibers of peptides and peptide-amphiphiles for tissue engineering, shape-memory polymers as molecular switches, and nanoporous membranes), and nanoscale microfabrication-based devices (eg, silicon microchips for drug release, and micromachined hollow needles and two-dimensional needle arrays from single crystal silicon), sensors, and laboratory diagnostics.¹²

Development of nanotechnology will provide clinical medicine new opportunities in different areas such as medical imaging, medical diagnosis, drug delivery, and cancer detection and management.

Medical imaging

Nanoparticles can provide significant improvements in traditional biologic imaging of cells and tissues using fluorescence microscopy as well as in modern magnetic resonance imaging (MRI) of various regions of the body.⁹ In optical imaging techniques, nanoparticles have helped to overcome the limitations of the organic fluorophores used currently which are not photostable and have low intensity. For example, quantum dots are resistant to photobleaching and photo, chemical, and metabolic degradation. In addition, superparamagnetic iron oxide nanoparticles have already been proven to be effective in increasing contrast in magnetic imaging, serving as a complement to gadolinium-based agents, with the ability to resolve the problem of altering the relaxation times of selected types of tissue or fluid within the body such as the kidney, brain, liver, and bone marrow. Superparamagnetic iron oxide nanoparticles have been used to detect small metastases in the lymph nodes, enabling patients with localized disease to be early treated by surgery without being exposed to radiation therapy.¹³ Iron oxide nanocrystals have been used to monitor gene expression or detect pathologies such as cancer, brain inflammation, arthritis, or atherosclerotic plaques that would not otherwise be detectable by conventional MRI.¹⁴

Medical diagnosis

The accurate targeting and quantification of molecules indicative of cellular disorders at the single-molecule level is

a demanding task for analysis systems. The combination of nanoparticles with other nanotechnology-based materials has the potential to address this emerging challenge and provide technologies that enable diagnosis at the level of single cells and single molecules.⁷ Antibodies, peptides, proteins, and nucleic acids are biologic molecules which could be linked covalently to functionalized nanoparticles which have been developed as nanoprobes for molecular detection. These functionalized nanoparticles can provide a direct rapid method of detection of infectious diseases and viruses in particular with high sensitivity.^{15,16}

Drug delivery

Medical therapies have become more tailored to both specific diseases and to patients on an individual basis in recent years. Most pharmaceutical agents have primary targets within cells and tissues; ideally, these agents should be preferentially delivered to their sites of action within the cell. Selective subcellular delivery is likely to have considerable therapeutic benefit.¹⁷ The benefits of this type of drug delivery include efficient encapsulation of the drug, successful delivery of drug to the targeted region of the body, and successful release of the drug. Developed nanoscale particles or molecules improve the bioavailability of the drug delivery both at specific places in the body and over a longer period of time.¹⁸ Drug delivery systems are based on nanoparticles which have a mesoscopic size range of 5–200 nm, allowing their unique interaction with biologic systems at the molecular level to produce multiple advantages, eg, reduced rate of drug clearance, alteration of the pharmacokinetics and biodistribution of the drug, passage of drugs through cell membranes and into the cell cytoplasm, and regulated drug release which can avoid the tissue damage caused by some drugs.¹⁹

There are numerous nanoparticles whose unifying feature is the nanometer scale size range. These include inorganic nanoparticles (such as metals, metal oxides, and metal sulfides), polymeric nanoparticles (such as gelatins, chitosan, polylactic acid, and polyglycolic acid), dendrimers, liposomes, nanocrystals, and nanotubes.¹⁷

Oncology

Nanotechnology is playing an increasingly revolutionary role in diagnosis, prognosis, prediction, and management of targeted cancer treatment. Development of cancer therapeutic agents has the two-fold aim of achieving greater target selectivity and better delivery efficiency. To produce minimal damage to normal tissue, therapeutic drugs have been conjugated with monoclonal antibodies (mAbs) that selectively

bind to antigens or receptors which are usually abundantly or uniquely expressed on the tumor cell surface. Nanoparticles have been shown to overcome both noncellular and cellular-based drug resistance and to increase selectivity of drugs toward cancer cells while reducing their toxicity toward normal tissues.²⁰ Several types of anticancer drugs, such as liposome-based formulations of several anticancer agents (stealth liposomal doxorubicin, liposomal doxorubicin, and liposomal daunorubicin) have been approved for the treatment of metastatic breast cancer.²¹ Nanoparticles can deliver the therapeutic agent to the interior of the cancer cell after binding to the tumor cell surface, triggering receptor-mediated endocytosis. Tumor-targeting ligands, such as antibodies, growth factors, or cytokines, have been used to facilitate the uptake of carriers into target cells.²²

Nanomedicine and stem cells

Stem cell therapy is a rapidly evolving area of research in regenerative medicine.^{23,24} Mesenchymal stem cells have received considerable attention in the field of cell therapy because of their ability to differentiate into various tissues of mesenchymal origin (eg, bone, cartilage, fat, muscle, marrow stroma, tendon, ligament, and other connective tissues),²⁵ making them excellent candidates for cell and tissue replacement therapies.^{26,27} However, there are still some obstacles in targeting stem cell therapy, including the problems in homing and fixing stem cells to their desired site and guiding extension of stem cells in specific directions. Nanoparticles have been used to overcome these challenges in the therapeutic application of stem cells.²⁸

Despite the wide range of applications of nanoparticles in the stem cell field, there is a dire lack of information concerning the impact of manufactured nanomaterials on human health and the environment.²⁹ This review reviews the most recent influences of nanoparticles on stem cell behavior. Biocompatibility of nanoparticles is the prerequisite for their applications in biomedicine, but this can be misleading due to the absence of criteria for evaluating their potential toxicity.³⁰

More than 10 million nanoparticles are ingested per person every day.³¹ The nanoparticles are small enough to penetrate even very small capillaries throughout the body, and can pass through biologic membranes, affecting cell function anywhere in the body. This consideration is of importance for stem cells, where the effects of nanoparticles on the potential for self-renewal and differentiation of stem cells is unknown. Data available from toxicity studies of nanoparticles, particularly in stem cells, are limited and

the molecular mechanisms of nanoparticle toxicity are still poorly understood.²⁹

Clinical and experimental studies indicate that a small size, a large surface area, and the ability to generate reactive oxygen species contributes to the potential of nanoparticles to induce cell injury.³² Braydich-Stolle et al²⁹ demonstrated that the cytotoxicity of nanoparticles is concentration-dependent. Dramatic changes occurred when cadmium oxide was added to germ-line stem cells. Within 48 hours of exposure at cadmium oxide concentrations of 1 µg/mL, stem cells were shown to shrink and become irregular, with significant inhibition of mitochondrial function. At concentrations of cadmium oxide higher than 5 µg/mL, stem cells became necrotic and detached from the culture dishes.

Development of new techniques to show accurate correlations between *in vitro* and *in vivo* studies is imperative to portray accurately nanoparticle effects. Moreover, toxicity studies are critical to establish the full *in vivo* potential of nanomedicine. Understanding the physicochemical, molecular, and physiologic processes of nanoparticles is important for nanomedicine to become a reliable and sustainable treatment modality.³³

Cellular uptake of nanoparticles by stem cells

Stem cells utilize various endocytic mechanisms for the uptake of nanoparticles, including phagocytosis, macropinocytosis, clathrin-dependent endocytosis, caveolae-dependent uptake, and non-clathrin/non-caveolae endocytosis.³⁴

With regard to silica nanoparticles, mesoporous silica conjugated with fluorescein isothiocyanate was efficiently internalized into human bone marrow mesenchymal stem cells even in short-term incubation.²⁶ The uptake of mesoporous silica nanoparticles was time- and concentration-dependent. Uptake began as early as 10 minutes after incubation and was relatively rapid within the first 1–2 hours of incubation, and a saturation uptake was achieved after 4 hours of incubation. Chung et al³⁵ demonstrated that internalization of mesoporous silica nanoparticles was mediated by both clathrin- and actin-dependent endocytosis. Huang et al³⁰ found that dynamic polymerization of actin filaments has a central role in the uptake of mesoporous silica nanoparticles, and found that inhibition of actin polymerization by cytochalasin D decreased their uptake. Ito et al³⁶ found that uptake of magnetic iron oxide cationic liposome nanoparticles began rapidly, and maximum uptake was achieved after 4 hours. The uptake of superparamagnetic iron oxide was shown to be mediated via endocytosis in

human mesenchymal stem cells.²⁵ Numerous studies have established a variety of techniques to deliver quantum dots into cells, such as microinjection, endocytic compartment, electroporation, liposome-mediated transfection, and special peptide delivery.³⁷ Chang et al³⁸ investigated cytoskeletal reorganization after the uptake of quantum dots which revealed the formation of wide and flat leading lamellipodia filled with a dense actin network in cells one day after addition. Liu et al³⁹ studied the endocytic mechanisms of 100 nm nanodiamond particles in stem cells and found that these particles were taken into the cells by macropinocytosis and clathrin-mediated endocytosis. The macropinocytosis was mediated by filopodia from cell membrane extension and cell-surface ruffling and invagination. It is possible that the mechanism of nanoparticle uptake by stem cells is influenced by the type, size, shape, concentration, and surface modification of the nanoparticles.

Location and distribution of nanoparticles in stem cells

After internalization of nanoparticles into stem cells, they become located in vesicles inside the cytoplasm. For instance, polystyrene particles ranging from 40 nm to over 120 nm were found scattered in the cell cytoplasm and cytoplasmic extension pseudopods.³¹ The nanoparticles were also located in the perinuclear region, forming rings around the cell nucleus. Nanodiamond particles of 100 nm were accumulated to develop a single nanodiamond cluster in a cytoplasmic vesicle, which contained several nanodiamond particles but they did not enter the nucleus.³⁹ In addition, after uptake into stem cells, superparamagnetic iron oxide nanoparticles were located inside the cytoplasm and vesicles, and could then be transferred to lysosomes, in which degradation of the nanoparticles could occur and free iron be released into the cytoplasm.^{40,41} In the quantum dots studies, Chang et al³⁷ found that delivered quantum dots had escaped from lysosome degradation at the beginning of the uptake. At 21 days, lysosome expression was enhanced and almost all the cellular quantum dots were observed in lysosome vesicles at this time.

Effects on viability, morphology, and proliferation of stem cells

The influences of different types of nanoparticles on the behavior of stem cells have been evaluated by several studies. Huang et al²⁶ and Chung et al³⁵ concluded that internalization of mesoporous silica nanoparticles conjugated with fluorescein isothiocyanate in human bone marrow

mesenchymal stem cells did not affect stem cell viability and proliferation. They proved that silica nanoparticles could escape from endolysosomal vesicles and retained their architectonic integrity after internalization. In addition, Huang et al³⁰ reported that silica nanoparticles can enhance actin polymerization induction in mesenchymal stem cells.

Ito et al³⁶ demonstrated that magnetic nanoparticles could be used to expand mesenchymal stem cells efficiently for clinical application. Mesenchymal stem cells incubated in osteogenic medium with magnetite iron oxide cationic liposomes changed their shape from fibroblastic to polygonal and formed calcium nodules. When mesenchymal stem cells were seeded at high density using magnetite cationic liposomes, there was a five-fold increase in the number of cells, compared with numbers seen in culture prepared without magnetite cationic liposomes. The survival rate of stem cells cultured in a medium containing superparamagnetic iron oxide was very high (97%–99%) indicating that superparamagnetic iron oxide did not affect stem cell viability.^{23,25,41,42} These observations suggest a promising role for nanomedicine in stem cell-related therapies. Selection of type and concentration of nanoparticles is critically important.

Kea et al⁴³ showed for the first time, that neural stem cells derived from bone marrow stroma of rhesus monkeys could be labeled *in vitro* with the superparamagnetic iron oxide contrast agent Feridex and Poly-L-Lysine without affecting morphology, cell cycle, telomerase activity, proliferation, and differentiation ability of the labeled cells. Huang et al²⁴ detected that ferucarbotran nanoparticles could promote the growth of human mesenchymal stem cells due to their ability to diminish intracellular H₂O₂ through intrinsic peroxidase-like activity. They reported that ferucarbotran could accelerate cell cycle progression mediated by free iron released from lysosomal degradation and involved alteration of iron on the expression of protein regulators of the cell cycle. Jung et al⁴⁴ studied the topologic and physical properties of the fibrin-poly(lactide-caprolactone) scaffolds. These nanoparticles were designed to improve stem cell seeding efficiency and cell in-growth, while enabling maintenance of the mechanical integrity and efficient delivery of mechanical signals to adherent cells and lead to a stronger biologic response.

On the other hand, embryonic stem cells cultured in low concentration (0.4 million/mL) polystyrene nanoparticles became mostly columnar and embryoid body-shaped. However, in high concentration (12.2 million/mL) nanoparticles, they became fibroblast-like and less squamous types. At the 24-hour time point, the presence of the nanoparticles reduced viability of the embryonic stem

cells by 40% and 30% in the low versus high relative concentration of nanoparticles, respectively. After six days of culture, there was a significantly smaller cell surface area associated with embryonic stem cells exposed to polystyrene nanoparticles compared with controls which was not concentration-dependent. This effect indicated the disruption of cytoskeletal development. In contrast, the nanoparticles did not have an effect on the size of the embryonic stem cell nucleus.³¹

Effect on stem cell differentiation

It is still controversial whether magnetic labeling with superparamagnetic iron oxide inhibits chondrogenic differentiation of mesenchymal stem cells.⁴⁵ Meanwhile, Heymer et al,²⁵ Delcroix et al,²³ and Wang et al⁴² detected that superparamagnetic iron oxide did not affect human mesenchymal stem cells undergoing adipogenic, osteogenic, or myogenic differentiation. In addition, naringin nanoparticles in concentrations (1–100 µg/mL) could enhance the proliferation and osteogenic differentiation of human bone mesenchymal stem cells.⁴⁶ Au et al⁴⁷ detected that superparamagnetic iron oxide labeling did not affect the calcium-handling properties of cardiomyocytes derived from embryonic stem cells. Moreover, transplantation of superparamagnetic iron oxide labeled embryonic stem cells via direct injection into infarcted myocardium resulted in significant improvement in heart function. These findings demonstrated the feasibility of *in vivo* tracking of embryonic stem cells using superparamagnetic iron oxide labeling and cardiac MRI, without affecting the cardiac differentiation potential and functional properties of embryonic stem cells.

In their study of silica nanoparticles, Huang et al³⁰ concluded that the uptake of mesoporous silica nanoparticles into human mesenchymal stem cells did not affect regular osteogenic differentiation of these cells. *In vitro* osteogenesis was successfully induced in the mesenchymal stem cells in highly chondrogenic synovium after the uptake of mesoporous silica nanoparticles.⁴⁸

Fibrin-poly(lactide-caprolactone) (PLCL) nanoparticles facilitated the upregulation of chondrogenesis marker genes and chondrogenic differentiation *in vitro*. The nanoparticle-fibrin-PLCL complex had chemical and physiologic characteristics designed to induce chondrogenic differentiation to sustain their lineage in the complex. *In vitro* and *in vivo* studies revealed that the complex developed effectively sustained chondrogenic differentiation and led to significant enhancement of the chondral extracellular matrix deposition on human adipogenic stem cells-fibrin-PLCL nanoparticle

complex constructs. This complex will be useful for *in situ* cartilage tissue engineering using human stem cells.⁴⁴

In contrast, Oliveira et al⁴⁹ showed that direct exposure to biphasic calcium phosphate particles impaired human mesenchymal stem cell osteogenic differentiation and bone matrix mineralization. They added that exposure to calcium-deficient apatite particles severely impaired human mesenchymal stem cell osteogenic maturation owing to the uptake of Ca²⁺ from the culture media.

Hussain et al⁵⁰ demonstrated that the level of cytotoxicity of nanoparticle-labeled stem cells depended on the type of the nanoparticles. Silver nanoparticles were detected to be the most toxic, and this cytotoxicity was mediated through oxidative stress. Carbon nanomaterials significantly impaired phagocytosis and induced cell death in alveolar macrophages.⁵¹ Polystyrene nanoparticles influenced viability and differentiation of embryonic stem cells to a minor extent.³¹

In vivo tracking of nanoparticle-labeled stem cells

Delivery of sufficient stem cells to the regions of interest with the smallest number of cells to untargeted regions is a prerequisite for maximizing the therapeutic benefits and minimizing possible unwanted effects of stem cell therapy. To monitor distribution, density, proliferation, and transdifferentiation of engrafted stem cells, reliable cellular imaging techniques are required.⁴²

Tracking the fate of stem cells employed in developmental biology and tissue regeneration is essential to understand how these cells participate in tissue repair. Inorganic probes with special physical properties have been developed using different systems of detectors such as quantum dots, light-emitting semiconductors, mesoporous silica nanoparticles, and superparamagnetic nanoparticle iron oxide.³⁸

Huang et al²⁶ concluded that the advantages of biocompatibility, durability, and higher efficiency in internalization of mesoporous silica nanoparticles made them a better vector for stem cell tracking than others currently used. Silica coating and polyethylene glycolation confers additional stability and biocompatibility to the magnetic ferrite nanoparticles. Organic dyes incorporated into the silica shell enabled the detection of multifunctional nanoparticle fluorescence.

Sykova et al⁵² tracked the fate of embryonic stem cells and bone marrow mesenchymal stem cells labeled with iron oxide nanoparticles in rats with cortical or spinal

cord lesions. Cells were either grafted intracerebrally and contralaterally to a cortical photochemical lesion, or injected intravenously. During the first post-transplantation week, grafted cells migrated to the lesion site in the cortex or spinal cord and were visible in the lesion on MR images as a hypointense signal, persisting for more than 30 days. Their studies demonstrated that MRI of grafted stem cells labeled with iron oxide nanoparticles is a useful method for evaluating cellular migration toward a lesion site.^{23,52} Furthermore, Kea et al⁴³ autografted Feridex-labeled neural stem cells derived from bone marrow stroma cells into the striatum of the rhesus monkey brain. They found that these cells survived, differentiated, and were incorporated into the brain, and could be reliably tracked using MRI. Concerning articular cartilage repair, labelling with superparamagnetic nanoparticle iron oxide had great potential to visualise human mesenchymal stem cells and track their migration after transplantation for articular cartilage repair with MRI following intra-articular injection.^{25,47} Using MRI, Lee et al⁵³ successfully tracked the multifunctional nanoparticle-labeled mesenchymal stem cells in the hearts of mice at seven days after induction of myocardial infarction. Thus, being able to monitor the fate of transplanted stem cells *in vivo* is crucial for developing successful cell therapies. MRI has afforded superb spatial resolution and repeated noninvasive imaging of magnetically nanoparticle-labeled stem cells, and appears to be the best modality for cell imaging.^{24,52}

Conclusion

Internalization of nanoparticles into stem cells had a significant influence on diverse aspects of cell activities. Viability, proliferation, differentiation, cytotoxicity, and *in vivo* tracking of stem cells labeled with nanoparticles have been shown to be type- and concentration-dependent. Therefore, more studies are needed to investigate the effects of different nanoparticles in directing stem cell behavior and should provide valuable information about the impact of nanoparticles in diagnostic and therapeutic applications.

Disclosures

The authors report no conflicts of interest in this work.

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