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REVIEW

The Story of Nanoparticles in Differentiation of Stem Cells into Neural Cells

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Abstract

Stem cells have been long looked at as possible therapeutic vehicles in regenerative medicine largely due to their multilineage differentiation potential and paracrine actions. Therefore, development of new procedures for the differentiation of stem cells into different cell types holds great potential for opening new opportunities in regenerative medicine. In addition to various methods for inducing stem cell differentiation, the utilization of nanomaterials for differentiation of stem cells has recently received considerable attention and has become a potential tool for such purpose. Multiple lines of evidence revealed that nanomaterial-based scaffolds, inorganic nanoparticles (NPs), and biodegradable polymers have led to significant progress in regulation of stem cell differentiation. Several studies indicated that different NPs including selenium, gold, graphene quantum dots (QDs) and silica could be employed for the regulation of differentiation of stem cells such as human mesenchymal stem cells (hMSCs). In addition, magnetic core–shell NPs could be applied for the regulation of neural stem cell (NSC) differentiation. Taken together, these findings suggested that NPs are potential candidates which could be utilized for the differentiation of stem cells into various cell types such as neural cells. Herein, we summarized the application of NPs for differentiation of stem cells into various cells in particular neural cells.

Keywords Nanomaterial · Nanoparticles · Stem cells · Differentiation · Neural cells

Introduction

Stem cells refer to undifferentiated cells with self-renewal capacity and differentiation potential to specialized functional cell types [1–4]. The classification of stem cells is based on the developmental stage. This stage is included two categories: somatic stem cells (SSCs) and embryonic stem cells (ESCs) [5], in which the latter is originated from the inner cell mass of blastocysts [6–8]. Induced pluripotent stem cells (iPS cells or iPSCs) are a class of pluripotent stem cells generated genetically from reprogramming of somatic cells with properties similar to the ESCs through the expression of determined genes and factors [9]. The highest differentiation ability and potent self-renewal capacity have been reported for pluripotent stem cells of ESCs and iPSCs [10, 11], whereas adult tissue-produced SSCs are less strong compared to ESCs and iPSCs, but are more accessible [12]. Recently, numerous types of SSCs have been separated from bone marrow, adipose tissues, cord blood, and neural tissues [13, 14]. Recent studies on tissue regeneration and engineering increasingly focused on various mesenchymal stem cells (MSCs) such as adipose-derived stem cells (ADSCs) and neural stem cells (NSCs), but with no observation of the ethical considerations of ESCs [1, 2].

Regulating and monitoring cell differentiation into target cell types highly affect the clinical applications of stem cells, in particular regarding tissue engineering and cell therapy [3, 4, 7, 15, 16]. Previously many researchers manipulated the differentiation of stem cells into different types of cells, including osteoblasts, neurons, adipocytes, and cardiomyocytes [17, 18]. The application of stem cell differentiation in stem cell therapy is restricted due to unsatisfactory differentiation efficiency and success rate. Moreover, the odds ratio of teratoma could be elevated because of undifferentiated ESCs following in vivo implantation. It is highlighting

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the importance of testing the differentiation of ESCs into specific lineages before implantation for a safe application in cell therapies [19, 20]. Therefore, the targeted differentiation of stem cells will be efficiently successful in directed cell types with the aid of further research and novel approaches. It has been shown that the current therapeutic approaches have various limitations [7]. Hence, developing new and effective approaches are needed.

Nanotechnology is a potent emerging science capable of overcoming the barriers related to the chemical techniques for differentiating stem cells. The development in regenerative medicine and tissue engineering dramatically depends on the advanced cell transplantation biology and new biomaterials. The nanotechnology deals with materials in sizes from 1 to 100 nm. Nanoparticles (NPs) vary in size from primary to natural forms and also in chemical, physical, biological, mechanical, optical, and electrical properties [21–23]. NPs can be classified based on their properties, sizes or shapes into different classes including metal NPs, fullerenes, polymeric NPs, and ceramic NPs. NPs size is very important; NPs have unique physiochemical properties as a result of their nanoscale size [24]. Since the nanoscale materials have the higher surface area and greater percentages of atoms at the surface, their higher surface energy is comparable with conventional materials; therefore the wettability and reactivity of the surface would be increased [25]. The optical properties of NPs are dependent on the size, which caused different colors due to absorption in the visible region. It is found that a 20-nm gold (Au), silver (Ag), platinum (Pt), and palladium (Pd) NPs have been characterized with wine red color, yellowish gray, black and dark black colors, respectively which can be utilized in bio-imaging applications [24].

During the past two decades, a growing number of nanomedicines (NMs) have received approval and many display potential for future clinical usage. The increasing demand of NMs has raised a question mark on their safety aspects on human health. It is important to assess the safety of NPs to achieve biocompatibility and also desired activity. Understanding the mechanisms of action and nanotoxicity of NPs, give insight into their safety issues. One of the important mechanisms of nanotoxicity is the generation of reactive oxygen species (ROS) and oxidative stress. These radical species may lead, altered cellular signaling, programmed cell death, and DNA damage. Thus, safer NPs can be designed by understanding their nanotoxicity mechanisms. The characterization of NPs is a crucial issue in determining the toxic potential of NPs. NPs related risks should be examined according to their potential routes to the human body [26].

Due to a variety of nanomedicines that include diverse manufactured NPs made from different materials, one could not make a generalized statement for the safety of NPS. There are some nanotherapeutics that are currently approved, such as Doxil and Abraxane; these drugs exhibit fewer side effects, while some others (e.g. metallic and carbon-based particles) tend to show toxicity [27].

Since NPs have distinct properties that cannot be predicted from the bulk material, appropriate assays for analyzing of toxicity of NPs should be selected for the evaluation of NPs cytotoxicity. Nevertheless, due to their size and surface properties, NPs behave differently. As NPs can aggregate, sediment, and also exhibit different diffusion dynamics; so, conventional test conditions would be unsuitable for NPs [28]. For example, the Ames test is generally used to measure the mutagenicity of agents but it failed to show genotoxicity of nanofibers which displayed genotoxicity in a mammalian assay [29]. Furthermore, it is revealed that carbon nanotubes interact with the tetrazolium salt of MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay which be used for viability measurements. NPs can therefore interfere with accuracy and sensitivity of some assays. Because NPs may interfere with some assays, multiple toxicity tests should be used to confirm safety assessment results [27, 28].

Besides suitable assays, the other important point is the use of proper doses. Use of inappropriate high doses of NPs in vitro which are not empirically administered in vivo, result in a false impression of toxicity. For that reason, it can be difficult to correlate in vitro doses to the in vivo conditions. Furthermore, it should be considered that different cell types display varying rates of NPs uptake in vivo. There are also some other aspects of NPs safety that should be considered such as purity of the NPs [27].

NPs are easily able to penetrate the cell and cause significantly different molecular variations owing to their small size and large surface area, predisposing medical applications, including diagnosis, drug delivery, tissue engineering, imaging, growth factor delivery and also different therapies [20–23]. Different nanomaterials are available in stem cell contexts, such as nanofibers, carbon nano-tubes (CNTs), quantum dots (QDs), metal NPs, and nano-substrates [30]. Accordingly, the present review article has been designed to summarize the applications of varied nano-materials involved in stem cell differentiation into various cells, as well as to highlight the use of NPs in stem cell differentiation into neuron cells.

Different Kinds of Nanoparticles

Researchers developed a variety of NPs based on their uses; for example, in diagnosis, imaging or treatment. Of course, a number of NPs are multi-purpose [21]. NPs have been categorized into two major classes of organic and inorganic. Organic NPs involve dendrimers, micelles, hybrid,

liposomes, and compact polymeric NPs. Inorganic NPs contain silica, fullerenes, gold, and quantum dots NPs. Nano-structures composed of amphiphilic molecules such as lipids or polymers are called micelles. In a case of their exposure to aqueous media, their hydrophobic groups will be concealed within the structure and the hydrophilic groups will be exposed. In other words, if they are in a lipid rich environment, the structures can be organized reversely [22]. Micelles hydrophobic core may load weakly water-soluble medicines, whereas amphiphilic medications correspond to micelles amphiphilic structures with the medicine polar groups in the neighborhood of the micelles hydrophilic groups. It was found that micelles are stable because of their hydrophilic shells. They also possess long-term circulation in the blood [23]. Morphology of a branched structure grown from 1 or higher cores characterizes as a dendrimer. Disadvantages of dendrimers are related to incorporating and releasing drugs, as well as timely and laborious synthesizing [24].

A liposome is a vesicle that has been completely composed of lipidic complexes. The commonest compounds are uni-lamellar liposomes with a size generally ranging between 100 and 800 nm. These spherical structures consist of amphiphilic complexes with higher generation costs and contents leakage. Complete biodegradability, compatibility, non-toxicity, and non-immunogenicity are the major benefits of these structures [25]. Compacted polymeric nanoparticles are nano-structures, which have been quietly fabricated of natural or synthetic polymers. In general, they have higher stability than liposomes, which leads to the longer localized drug delivery for several weeks and lower leakage of drugs [22]. Ultimately, there may be a covalent linkage between such polymeric nano-structures and treatment agents. As an alternative, surfaces of the NPs can absorb, dissolve, entrap it in the structure of NPs (nano-spheres), and encapsulated within a polymeric shell (nano-capsules) [22, 26]. The core–shell polymer-lipid hybrid NPs are one of the intermediary types of NPs. There are a bio-degradable hydrophob polymeric core and a lipid outer mono-layer into its structure [68]. On the other hand, we may use an internal polymeric core enclosed by an exterior lipid bilayer [27, 28]. Core–shell polymer lipid hybrid NPs enjoy supplementary features of the two structures; that is, high stability and higher yield of medicine encapsulation, as well as the superiority of in vivo cellular delivery efficiency. As one of the medicine delivery procedures, encapsulation of the medicine is generally performed in the polymeric core, while the external layer of the lipid declines the rates of diffusing water, and lowers the kinetics of releasing medicine [31]. On the other hand, hybrid NPs are possibly fabricated by an inorganic core enclosed by an organic shell; that is, a metal core enclosed by a polymeric shell [32]. Luminescent semiconductor crystals include quantum dots, nano-metric multi-functional inorganic fluorophores applied in imaging, detecting, and targeting [33, 34]. These crystals are composed of the components from II–VI or III–V groups and their structure is usually on the basis of cadmium sulfide (CdS) and cadmium selenide (CdSe), which may be greatly poisonous [35]. In comparison to the conventional fluorophores, such as organic colors and fluorescent proteins, quantum dots take advantage of wide adsorption ranges and narrow emission spectrum. Indeed, their size emission can be adjusted via distinct wavelengths on a broad range of optical spectra. In addition, quantum dots have higher photostability and considerable resistance to photo-bleaching [36, 37]. They are also used because of their distinct physical and chemical features, size, and strongly compacted structure [34]. Moreover, NPs may be readily fabricated from carbon molecules with different regular and steady forms known as fullerenes (an allotrope of carbon) [38]. One of the commonest fullerenes with a rigid icosahedron with 60 carbon atoms is buckminsterfullerene (C60). Single bonds of its structure create a pentagon, and double bonds create hexagons [39]. However, distinctive optical, electrical, and magnetic features (e.g., super-conductivity) can resolve the drawbacks of fullerenes that include lower solubility in the organic solvents. For this reason, they are considered prominent instruments for imaging and diagnosing [40, 41]. Moreover, NPs may be produced by using inorganic substances like silica, gold, platinum, and silver. A variety of techniques are used to prepare inorganic NPs, which form a systematic and robust 3D array with metal or atoms with covalent linkage [42]. In spite of organic NPs, in vivo conditions do not affect inorganic features, including dimensions and shape [42]. Nonetheless, researchers should consider the disadvantages of inorganic NPs. In addition, the impossible loading of medicines in their structures and their probable negative impacts on blood should be studied for metal NPs [43, 44]. Yet, their higher capacity as magnetic responsive nano-entities is very important, so that it was widely studied by the authors [45]. Alternatively, if the reactive oxygen specimens and the glutathione increase, and decrease respectively, silica NPs will apply a cytotoxic impact [46].

Cellular Uptake of Nanoparticles

As NPs have small sizes, they may face various kinds of cells and experience translocation across membrane obstacles in an organism. Prior studies demonstrated NPs entering into cells, so that NPs with diameters <40 nm may introduce nucleus of the cell, and those below 35 nm may also traverse the blood–brain obstacle [44, 45]. Phagocytosis, nonclathrin and non-caveolin mediated endocytosis, clathrin-mediated endocytosis, macro-pinocytosis, and caveolin-mediated endocytosis are among a lot of pathways explored for

cellular uptake of NPs (Fig. 1) [46, 47]. Following cellular uptake of NPs, the other important matter is the intracellular trafficking. The final destination of NPs within cellular compartments determines the cytotoxicity and therapeutic efficacy of NPs [47]. After internalizing NPs, they would be encountered in early endosomes which are membrane-bounded intracellular vesicles. Endosomes are classified into three types including early endosomes, late endosomes and recycling endosomes [48].

Early endosomes carry the cargo to the cellular destination. Recycling endosomes recycle a part of the cargo to the plasma membrane. Early endosomes convert into late endosomes through the maturation process. Endolysosomal vesicles are formed by integrating late endosomes with lysosomes; these vesicles contain hydrolytic enzymes that degrade the trapped NPs [49]. Nevertheless, some NPs can escape this pathway; they are released into the cytoplasm [50]. Autophagy is another degradation pathway that plays a crucial role in the intracellular fate of NPs. In autophagy, autophagosome surrounds cytoplasmic contents such as dysfunctional organelles and aggregated proteins and their delivery to the lysosome [51]. Johnston and co-workers studied the intracellular fate of NPs in hepatocyte. They were internalized by hepatocytes in size, time and serum-dependent manner. It was found that NPs accumulates in the bile canaliculi and can be eliminated by bile [52].

Various biological responses may be induced by interacting between NPs and cells in vitro or in vivo. For example, in a case of the exposure of the cells to the NPs in vitro, the cell cycles and appearance of apoptotic and inflammatory markers may be modified [48, 49]. In addition, NPs may damage the cells, form ROS, increase the specific cytokine formation, and generate disorders in cell behaviors, including cell migration, adhesion, and differentiation [50–52]. Hence, systematic evaluation and understanding of the interaction between NPs and live systems are crucial for developing bio-compatible NPs. Reviewing the interplays between NPs and cells in vitro provides a swift simple attitude to discover cellular responses to a particular dosage of NPs, exposure duration, and intra-cellular related pathways for various kinds of cells. Reports indicated the effect of numerous parameters, including NPs properties; for example, dimension, morphology, composition, and surface charge, extra-cellular matrix medium (e.g., pH, temperature, the concentration of ion), type of cells, and protein absorption on the cellular uptake [53–56]. Here, the effect of NPs properties and absorption of proteins are emphasized, because extra-cellular matrix (ECM) medium and different kinds of cells can be readily repaired. It has been showed that NPs exert their effects via affecting various cellular and molecular targets such as microRNAs [23]. The modulation of miRNAs expression

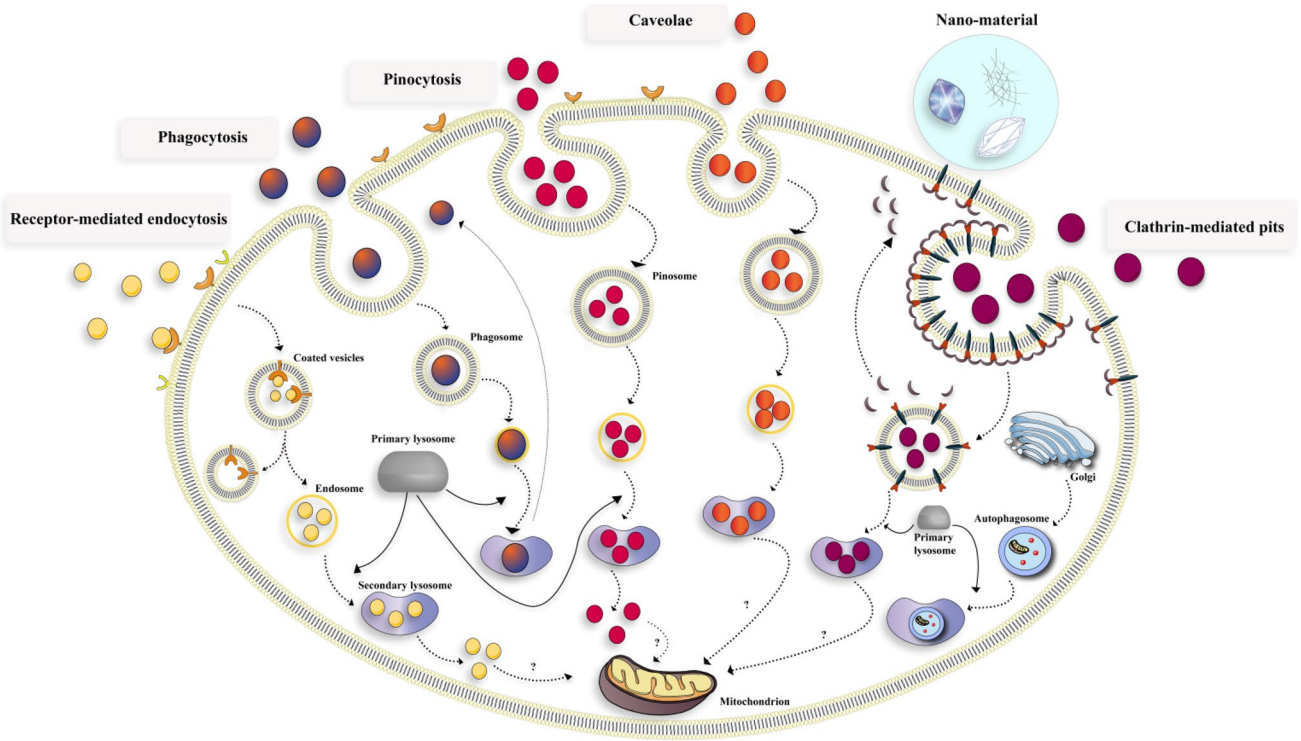

Fig. 1 Different mechanisms of endocytosis; including Phagocytosis, nonclathrin- and non-caveolin mediated endocytosis, clathrin mediated endocytosis, macro-pinocytosis, and caveolin-mediated endocytosis

is associated with inhibition of disease progression [15, 53–58].

Nanoparticles and Stem Cell Differentiation

One of the functions of the nanomaterials is playing a role as a nano-carrier in the cell to deliver drugs or nucleic acids involved in stem cell differentiation. Sometimes, there is need for appropriate vector to carry the drugs or chemicals with poor solubility, short half-life, and poor penetration as well as exogenous nucleic acids with unsuccessful intracellular penetration [59, 60]. The intracellular enzymes rapidly degrade the exogenous nucleic acids or bio-macromolecules following the entry into the cells and also metabolize the small-molecule drugs [60]. The unique biomechanical properties promisingly enable some NPs to facilitate the differentiation of stem cells, such as AuNPs, AgNPs, GO, CNTs and silica NPs [61–65]. The NPs can enter easily into cytoplasm across the cell membranes and so alter targeted cellular signaling pathways responsible for differentiation [66, 67]. Different nano-materials could affect surface ligand and various cell types which inhibit/activate a sequence of cellular pathways. Based on Fig. 2, the mechanisms of differentiation are affected significantly by various physicochemical properties of nanomaterials.

Some signaling pathways in stem cells are activated mechanically by NPs, hereby stimulating the differentiation process. The optimal size of NPs for differentiation of stem cells varies from 20 nm to 70 nm, because of size-dependent cellular uptake rates [68–70]. The 50-nm NPs revealed higher levels of internalization by cells, whereas smaller NPs are more cytotoxic and larger NPs are less efficient [71, 72]. The morphology of NPs can also influence their penetration into the cells, which affects the differentiation of stem cells [69]. Nanospheres are much likely to enter the cells compared to the nanorods, with the same size [71]. It can be claimed that the size and the shape of NPs determine their capacity to be taken up by the cells; this shows the importance of these two parameters in the differentiation processes. The NPs with different size and shape through inducing mechanical signals can affect the differentiation of stem cells.

Other important parameters of the nanomaterials to conduct the differentiation of stem cells are their charge and the specific chemical moieties. The biomolecules, including proteins, nucleic acids, lipids and polysaccharides, contain abundantly functional chemical domains, such as amines ($–NH_2$), hydroxyl (–OH), and carboxyl (–COOH), which

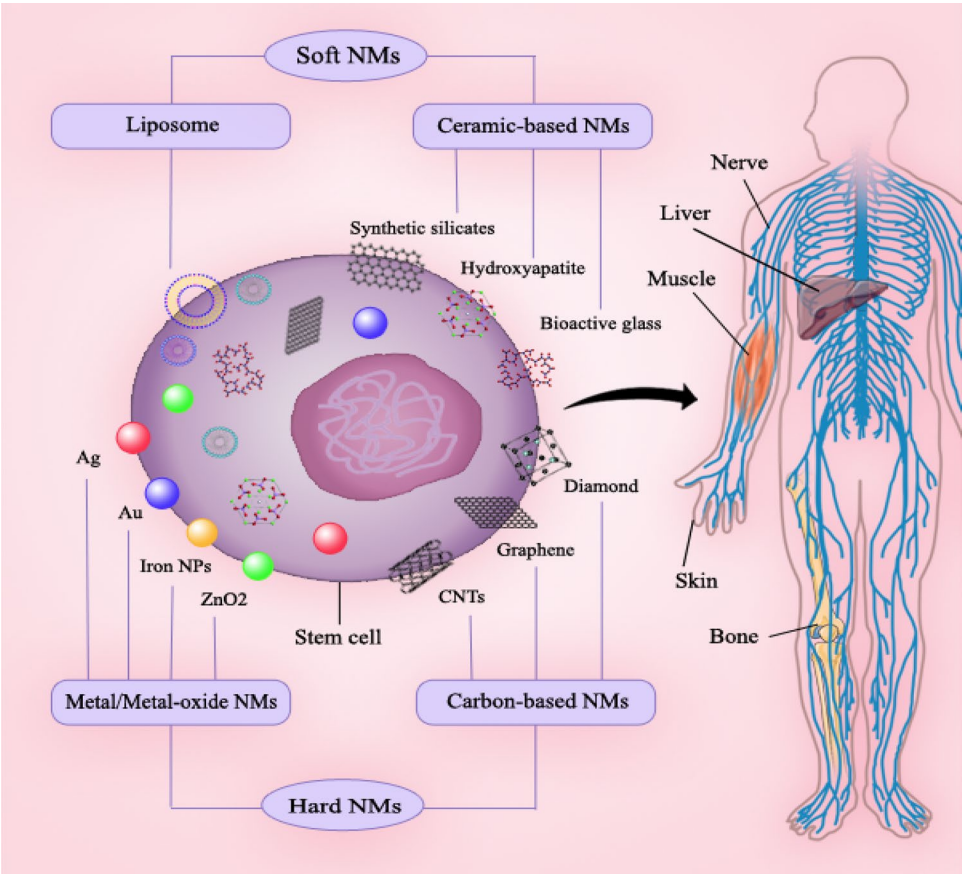

Fig. 2 A schematic picture of nanomaterial interactions with stem cells. Physicochemical properties of soft NMs and hard NMs affect the differentiation pathway

highly influence the behavior and the differentiation of stem cells [73]. According to a study, osteogenic differentiation was blocked with COOH–AuNPs treatment, but not with $–NH_2$ and –OH groups functionalizing AuNPs [74]. The uptake of NPs can be influenced by various surface charges and groups so that higher cell uptake and cytotoxicity has been reported for positively charged NPs [71]. There is also an interconnection between most physicochemical factors. For example, the size-dependent uptake can be the reason for the effect of charge. The complexity is enhanced due to additional surface coatings as well.

There are various cell-signaling cascades that occur due to varied surface coating of nanomaterials. For example, the p38 MAPK pathway is involved in enhancing the osteogenic differentiation of MSCs by AuNPs, while the Wnt/β-catenin signaling pathway in hADSCs is activated by chitosan-conjugated AuNPs [63, 75]. The microenvironment and also the interaction of biomolecules and stem cells can be dramatically mimicked through nanomaterials with specific surface modifications [74]. Some serum proteins and bioactive molecules, such as cytokines and growth factors in the physiological environment, can be absorbed on nanomaterials, thereby increasing the differentiation of stem cells [9, 76, 77]. The uptake of differentiation factors is affected by the surface charge and the size of nanomaterials, probably because of various electrostatic interactions and area-to-volume ratio [78].

The involvement of most physical and chemical parameters makes it difficult to explain explicitly the interactions of NPs and stem cells. There is a need for further research to better understand the fundamental principles of the differences in the internalized NPs for the differentiation of stem cells. Despite the fact that these nanomaterials are non-cytotoxic and enhance stem cell differentiation into specific cell types, a majority of the nanomaterials cannot be degraded apparently after penetration into cells, underlining the necessity for extensive and pre-designed investigations to evaluate their long-term biological safety.

The NPs are of the best in vitro and in vivo carriers for nucleic acids/drug delivery [79]. This feature is due to their biocompatibility and ease of fictionalization for targeting stem cells and releasing payloads in the cytoplasm [79], thus representing NPs as ideal carriers for intracellular delivery of drugs, nucleic acids, growth factors and other biomolecules in the differentiation of stem cells [80–82].

MiRNAs are important epigenetic regulators which have several roles in the pathological and physiological conditions [83–89]. It has been shown that dysregulation of these molecules are associated with the initiation and progression of various diseases such as diabetes, cancer, cardiovascular diseases, viral infections and so on [1, 90–95]. Hence, it seems that targeting miRNAs could be used in the treatment of several diseases [93, 96–102].

One of the biodegradable nanocarriers for miRNA delivery is chitosan in the regulation of the osteogenic differentiation of MSCs, while different polymeric NPs can also deliver miRNAs [103, 104]. Although the drug delivery is fulfilled mostly by inorganic NPs, such as AuNPs, AgNPs and silica NPs, owing to their load capacity, this phenomenon has been restricted because of their non-biodegradability [105]. The AgNPs acts as a carrier for miR-148b delivery and mesoporous silica NPs for Amino Acid (AA) delivery [106, 107]. Various bioactive payloads can be delivered via NPs without any adverse effect on cell activity but with significant influence on differentiation. The certain signaling cascades are activated inside the cells because of payloads released by the drug-loaded nanomaterials entered into the cytoplasm. The surface payloads of nanomaterials mainly direct the mechanisms of differentiation. Further studies can focus on the NPs with biocompatibility and biodegradability capable of targeting stem cells, releasing payloads in the cytoplasm, and inducing signaling cascade activation [66].

Table 1 summarizes the role of nanomaterials in the differentiation of stem cells. Different specific lineages, including osteoblasts, neural cells, cardiocytes, chondrocytes and hepatocyte-like cells, can be produced by integrating the nanomaterials, and the stem cells. Each nanomaterial is material with multipurpose applications in the differentiation of various stem cells, including MSCs, ESCs, ADSCs, NSCs, and iPSCs, into different lineages. For instance, although silica NPs are unable to influence positively the differentiation of stem cells, but act as nanocarriers to deliver insulin to rMSCs for adipogenic differentiation [108], or AA to hESCs for cardiac differentiation [107]. Moreover, the aligned single-walled carbon nanotubes (SWCNTs) can direct positively the osteogenic differentiation of hMSCs [109]. The carboxylated multi-walled carbon nanotubes (MWCNTs) enhance the neural differentiation of hBMSCs, and the poly (ε-caprolactone)-functioned SWCNT scaffolds promote the cardiac differentiation of rMSCs [62, 110].

Nanoparticles and Neuronal Differentiation

One of the concerns in modern society is related to brain-associated disorders, including neurodegenerative diseases, stroke, and traumatic injuries [145]. The regulation of proliferation, differentiation and migration of neural stem cells (NSCs) is considered as a promising regenerative/therapeutic strategy due to their differentiation into new neural cells, including neurons. The bioactivity of NSCs can be efficiently controlled by the new NPs plus pharmaceuticals [146]. Accordingly, the neural tissue engineering has been improved due to advances in the design and construction of nanomaterials. Different synthetic polymers are available with unique consistency

Table 1 Nanomatrials and differentiation of various types of stem cells

Nanomaterial (s)	Type of stem cells	Cell lineages generated	Chemical modifications/components	Citation (s)
PLGA- NPs	Neural stem cells	Neuronal differentiation	miR-124	[111, 112]
PBAEs/DNA nanoparticles	hNSCs	Neuronal differentiation	neurogenin-2	[113]
Mesoporous silica nanoparticle	Neural stem cells	Neural differentiation		[114]
GO	mESCs	Dopamine neurons		[64]
GD-ws-SWCNT	SCAP	Neuronal differentiation		[115]
IONPs	hMSCs	Neuronal, adipogenic and osteogenic lineages	HSA/FGF2	[116]
DNA nanotubes	mNSCs	Neurons	Peptide RGDS	[117]
Polymeric nanoparticles	mNSCs/hiPSCs/mouse SVZ stem cells	Neuronal differentiation	RA	[118]
Polyethyleneimine complex	mESCs	Neuronal differentiation	RA	[119]
Polymeric nanoparticles	mNSCs	Neurons	siSOX9 and RA	[120]
GR/TiO_2 heterojunction	hNSCs	Neurons		[121]
GR	hNSCs	Neurons	Laminin-coated	[122]
rGO-collagen hybrid scaffold	rBMSCs	Neurons		[123]
MWCNTs	hBMSCs	Neurons	Carboxylated	[62]
Xanthan and magnetite nanoparticles hybrid scaffolds	mESCs	Neurons		[124]
AuNPs	mMSCs/hADSCs/hMSCs	Osteogenic differentiation		[63]
Nano-coated surfaces include Zn, Ag and/or Cu	hMSCs	Osteogenic differentiation		[125]
AuNPs	hADSCs	Osteogenic differentiation	Chitosan	[75]
AgNPs	mMSCs	Osteogenic differentiation		[65]
AgNPs	hUSCs	Osteogenic differentiation		[126]
AgNPs	hADSCs	Osteogenic differentiation	miR-148	[106]
IONPs	hBMSCs	Osteogenic differentiation		[127]
Chitosan-based-microRNA nanoparticles	rMSCs	Osteogenic differentiation	AntimiR-138	[128]
TiO_2-coated CoCrMo	hMSCs	Osteogenic differentiation		[129]
TiO_2 scaffolds	hMSCs	Osteogenic differentiation		[17]
GR	hMSCs	Osteogenic differentiation		[130]
GO-PLGA nanofiber scaffolds	hMSCs	Osteogenic differentiation		[131]
Graphene nanogrids	hMSCs	Osteogenic differentiation		[132]
Aligned SWCNTs	hMSCs	Osteogenic differentiation		[109]
MWCNTs	hMSCs	Osteogenic differentiation	PEG	[133]
PLLA/PBLG/collagen nanofibrous	Rabbits-ADSCs	Osteoblasts and adipocytes		[134]
GQD	rBMSCs	Osteoblasts and adipocytes		[135]
Silica nanoparticles	hESCs	Cardiac differentiation	AA	[107]
AuNPs-loaded functionalized nanofibers	hMSCs	Cardiac differentiation	PCL/SF/AV/VitB12/GNP fibers	[136]
AuNPs-loaded hybrid nanofibers	hMSCs	Cardiac differentiation	BSA/PVA scaffolds	[137]
MWCNTs	hMSCs	Cardiac differentiation	Poly(ε-caprolactone)	[110]
PLGA/nHAp Scaffold	MSCs	Chondrogenic differentiation		[138]
PCL Scaffold	MSCs	Chondrogenic differentiation		[139]
PLLA/nHAp	MSCs	Chondrogenic differentiation		[140]
Silica nanoparticles	rMSCs	Adipogenic differentiation	Insulin	[108]
SWCNTs	rMSCs	Adipogenesis		[141]
Mesoporous silica	miPSCs	Hepatocyte-like cells	HNF3β plasmid DNA	[142]
Chitosan nanoparticles	mBMSCs	Hepatocytes	Hepatocyte growth factor	[80]

Table 1 (continued)

Nanomaterial (s)	Type of stem cells	Cell lineages generated	Chemical modifications/components	Citation (s)
MWCNTs-incorporated nanocomposite scaffolds	hBMSCs	Cartilage regeneration		[143]
SPIONs	ESCs	Myogenic differentiation		[144]

and properties, including polyethyleneimine (PEI) and poly- L-ornithine (PLO), which are able to invigorate the growth and the adhesion of neural cells [147]. High potential in the long-term neuronal differentiation of human neural stem cells (hNSCs) without supplements inducing differentiation has been demonstrated for graphene film which was synthesized and transferred onto a glass substrate [148, 149]. This ability is mediated by its capacity to enhance the adhesion of NSCs and so the creation of proper microenvironment and also electrical coupling with neural cells that resulting in neural stimulation [148]. The differentiation of hNSCs by graphene film is predominantly tended to neuronal lineage rather than glial ones. The differentiation of NSCs in the brain sub-ventricular zone (SVZ) was enhanced by retinoic acid (RA)-loaded PEI/dextran sulfate (DS) NPs [150], providing the internalization and the intracellular release of RA to predispose the interaction with the RA receptor (RAR), the activation of stress-activated protein kinases (SAPK) and also JNK signaling pathways. Evidence showed neuronal differentiation in primary neurons and immature neuronal cell lines in exposure to AuNPs-loaded electrospun nanofiber scaffold, but no neurite growth or branching was observed for cells grown on AuNPs-free scaffolds. AuNPs improved neurite lengths from the soma, the total length of the neurite branches and branch complexity as well [151]. Moreover, the CNTs have been proposed to be applied in neuroscience in relation to the enhancement of neuron-related signaling, owing to their special properties, including ultra-high electron mobility and conductivity, surface roughness, and porosity [152]. A study employed thin films of poly (acrylic acid)-grafted CNTs to improve viability, adhesion, mature neurite growth and branching of hESCs, resulted in a twofold greater effect compared to the conventional neuronal substratum of PLO [153]. Adhesion, growth factor adsorption and differentiation of ESCs were enhanced in a study using CNT-based nano-fibrillar surfaces, which had properties similar to ECM [154]. It also reported a cue, probably due to low acidic and high hydrophobic nature of poly (methacrylic acid), predisposing the binding of ESCs colonies strongly with differentiation into mature neuronal cells [154]. According to an in vitro study, the composite-contained collagen-CNTs played a role of a matrix to trigger early neuronal differentiation in about 90% of ESCs [155], and the neuronal differentiation of ESCs was increased efficiently by the CNTs. In fact, these results on nanomaterials would open a new window to treat the nerve injuries.

Conclusion

Further development and improvement are needed for the existing approaches related to damaged tissue regeneration. Among which the NPs are important to modify the scaffolds and trigger the intricate characterizations of various tissues such as bone, which are appropriate microenvironment for proliferation, adherence, and differentiation of the targeted cells. The spatial–temporal release and kinetics of central factors responsible for iPSC reprogramming and differentiation can be modulated by NPs, thereby improving their efficiency and safety. The potential of NPs to deliver factors to the sub-cellular target sites is dependent on particle size, uptake, and the surface area-to-volume ratio [30]. The NPs are able to interact with stem cells and switch their differentiation into different lineages by modulating certain cellular signaling pathways, differentiation-related factors, cell proliferation, and adherence. Various NPs such as silica NPs, graphene, and poly butyl cyanoacrylate NPs have been used for differentiation of iPSCs to multiple cell lineages including endodermal cells [156], ectodermal cells [157], and neuronal cell [158], respectively.

Further research is needed for knowing better the exact principles of NPs in the differentiation of stem cells and the modulation of stem cell behaviors. Additionally, it is essential to consider the cytotoxicity of some NPs at certain levels during their application. Therefore, meticulous studies should be conducted to find out the risks associated with the use of such cytotoxic NPs. Moreover, the comprehensive studies are needed to be carried out to prove the interactions of stem cells with topographical properties of NPs. Finally, it can be concluded that the NPs can be utilized in special treatments for the damaged tissue regeneration through the modulation of stem cell differentiation.

References

1. Rabieian R, Boshtam M, Zareei M, Kouhpayeh S, Masoudifar A, Mirzaei H (2018) Plasminogen activator inhibitor Type-1 as a regulator of fibrosis. J Cell BioChem 119:17–27
2. Moradian Tehrani R, Verdi J, Noureddini M, Salehi R, Salarinia R, Mosalaei M, Simonian M, Alani B, Ghiasi MR, Jaafari MR,

Mirzaei HR, Mirzaei H (2018) Mesenchymal stem cells: a new platform for targeting suicide genes in cancer. J Cell Physiol 233:3831–3845
3. Goradel NH, Hour FG, Negahdari B, Malekshahi ZV, Hashemzehi M, Masoudifar A, Mirzaei H (2018) Stem cell therapy: a new therapeutic option for cardiovascular diseases. J Cell BioChem 119:95–104
4. Mohammadi M, Jaafari MR, Mirzaei HR, Mirzaei H (2016) Mesenchymal stem cell: a new horizon in cancer gene therapy. Cancer Gene Ther 23:285–286
5. Meng X, Ichim TE, Zhong J, Rogers A, Yin Z, Jackson J, Wang H, Ge W, Bogin V, Chan KW (2007) Endometrial regenerative cells: a novel stem cell population. J Transl Med 5:57
6. Thomson JA, Itskovitz-Eldor J, Shapiro SS, Waknitz MA, Swiergiel JJ, Marshall VS, Jones JM (1998) Embryonic stem cell lines derived from human blastocysts. Science 282:1145–1147
7. Gholamin S, Mirzaei H (2018) GD2-targeted immunotherapy and potential value of circulating microRNAs in neuroblastoma. J Cell Physiol 233:866–879
8. Mirzaei H, Sahebkar A, Avan A, Jaafari MR, Salehi R, Salehi H, Baharvand H, Rezaei A, Hadjati J, Pawelek JM, Mirzaei HR (2016) Application of mesenchymal stem cells in melanoma: a potential therapeutic strategy for delivery of targeted agents. Curr Med Chem 23:455–463
9. Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126:663–676
10. Yu J, Vodyanik MA, Smuga-Otto K, Antosiewicz-Bourget J, Frane JL, Tian S, Nie J, Jonsdottir GA, Ruotti V, Stewart R, Slukvin II, Thomson JA (2007) Induced pluripotent stem cell lines derived from human somatic cells. Science 318:1917–1920
11. Okita K, Ichisaka T, Yamanaka S (2007) Generation of germline-competent induced pluripotent stem cells. Nature 448:313–317
12. McMurray RJ, Dalby MJ, Tsimbouri PM (2015) Using biomaterials to study stem cell mechanotransduction, growth and differentiation. J Tissue Eng Regen Med 9:528–539
13. Witkowska-Zimny M, Walenko K, Walkiewicz AE, Pojda Z, Przybylski J, Lewandowska-Szumiel M (2012) Effect of substrate stiffness on differentiation of umbilical cord stem cells. Acta Biochim Pol 59:261–264
14. Lee MH, Goralczyk AG, Kriszt R, Ang XM, Badowski C, Li Y, Summers SA, Toh SA, Yassin MS, Shabbir A, Sheppard A, Raghunath M (2016) ECM microenvironment unlocks brown adipogenic potential of adult human bone marrow-derived MSCs. Sci Rep 6:21173
15. Fathullahzadeh S, Mirzaei H, Honardoost MA, Sahebkar A, Salehi M (2016) Circulating microRNA-192 as a diagnostic biomarker in human chronic lymphocytic leukemia. Cancer Gene Ther 23:327–332
16. Cha C, Liechty WB, Khademhosseini A, Peppas NA (2012) Designing biomaterials to direct stem cell fate. ACS Nano 6:9353–9358
17. Pullisaar H, Verket A, Szoke K, Tiainen H, Haugen HJ, Brinchmann JE, Reseland JE, Ostrup E (2015) Alginate hydrogel enriched with enamel matrix derivative to target osteogenic cell differentiation in TiO_2 scaffolds. J Tissue Eng. https://doi.org/10.1177/2041731415575870
18. Lee WC, Lim CH, Shi H, Tang LA, Wang Y, Lim CT, Loh KP (2011) Origin of enhanced stem cell growth and differentiation on graphene and graphene oxide. ACS Nano 5:7334–7341
19. Przyborski SA (2005) Differentiation of human embryonic stem cells after transplantation in immune-deficient mice. Stem cells (Dayton, Ohio) 23:1242–1250
20. Wang Y, Yang D, Song L, Li T, Yang J, Zhang X, Le W (2012) Mifepristone-inducible caspase-1 expression in mouse embryonic stem cells eliminates tumor formation but spares differentiated cells in vitro and in vivo. Stem cells (Dayton, Ohio) 30:169–179
21. Daniel M-C, Astruc D (2004) Gold nanoparticles: assembly, supramolecular chemistry, quantum-size-related properties, and applications toward biology, catalysis, and nanotechnology. Chem Rev 104:293–346
22. Iravani S, Korbekandi H, Mirmohammadi SV, Zolfaghari B (2014) Synthesis of silver nanoparticles: chemical, physical and biological methods. Res Pharm Sci 9:385
23. Hashemi Goradel N, Ghiyami-Hour F, Jahangiri S, Negahdari B, Sahebkar A, Masoudifar A, Mirzaei H (2018) Nanoparticles as new tools for inhibition of cancer angiogenesis. J Cell Physiol 233:2902–2910
24. Singh S, Zafar A, Khan S, Naseem I (2017) Towards therapeutic advances in melanoma management: an overview. Life Sci 174:50–58
25. Mucalo M (2015) Hydroxyapatite (HAp) for biomedical applications. Elsevier, Amsterdam
26. Jain A, Ranjan S, Dasgupta N, Ramalingam C (2018) Nanomaterials in food and agriculture: an overview on their safety concerns and regulatory issues. Crit Rev Food Sci Nutr 58:297–317
27. Wolfram J, Zhu M, Yang Y, Shen J, Gentile E, Paolino D, Fresta M, Nie G, Chen C, Shen H (2015) Safety of nanoparticles in medicine. Curr Drug Targets 16:1671–1681
28. Oberdörster G (2010) Safety assessment for nanotechnology and nanomedicine: concepts of nanotoxicology. J Intern Med 267:89–105
29. Clift MJ, Raemy DO, Endes C, Ali Z, Lehmann AD, Brandenberger C, Petri-Fink A, Wick P, Parak WJ, Gehr P (2013) Can the Ames test provide an insight into nano-object mutagenicity? Investigating the interaction between nano-objects and bacteria. Nanotoxicology 7:1373–1385
30. Dayem AA, Choi HY, Yang GM, Kim K, Saha SK, Kim JH, Cho SG (2016) The potential of nanoparticles in stem cell differentiation and further therapeutic applications. Biotechnol J 11:1550–1560
31. Hadinoto K, Sundaresan A, Cheow WS (2013) Lipid-polymer hybrid nanoparticles as a new generation therapeutic delivery platform: a review. Eur J Pharm Biopharm 85:427–443
32. Parveen S, Misra R, Sahoo SK (2012) Nanoparticles: a boon to drug delivery, therapeutics, diagnostics and imaging. Nanomed Nanotechnol Biol Med 8:147–166
33. Michalet X, Pinaud FF, Bentolila LA, Tsay JM, Doose S, Li JJ, Sundaresan G, Wu AM, Gambhir SS, Weiss S (2005) Quantum dots for live cells, in vivo imaging, and diagnostics. Science (New York, NY) 307:538–544
34. Ghasemi Y, Peymani P, Afifi S (2009) Quantum dot: magic nanoparticle for imaging, detection and targeting. Acta Niomed 80:156–165
35. Fernandez-Fernandez A, Manchanda R, McGoron AJ (2011) Theranostic applications of nanomaterials in cancer: drug delivery, image-guided therapy, and multifunctional platforms. Appl Biochem Biotechnol 165:1628–1651
36. Dubertret B, Skourides P, Norris DJ, Noireaux V, Brivanlou AH, Libchaber A (2002) In vivo imaging of quantum dots encapsulated in phospholipid micelles. Science (New York, NY) 298:1759–1762
37. Bailey RE, Nie S (2003) Alloyed semiconductor quantum dots: tuning the optical properties without changing the particle size. J Am Chem Soc 125:7100–7106
38. Chen Z, Ma L, Liu Y, Chen C (2012) Applications of functionalized fullerenes in tumor theranostics. Theranostics 2:238–250
39. Ma H, Liang X-J (2010) Fullerenes as unique nanopharmaceuticals for disease treatment. Sci China Chem 53:2233–2240

40. Bosi S, Da Ros T, Spalluto G, Prato M (2003) Fullerene derivatives: an attractive tool for biological applications. Eur J Med Chem 38:913–923
41. Hebard AF (1992) Superconductivity in doped fullerenes. Phys Today 45:26–32
42. Kim T, Hyeon T (2013) Applications of inorganic nanoparticles as therapeutic agents. Nanotechnology 25:012001
43. Mishra D, Hubenak JR, Mathur AB (2013) Nanoparticle systems as tools to improve drug delivery and therapeutic efficacy. J Biomed Mater Res, Part A 101:3646–3660
44. De Jong WH, Borm PJ (2008) Drug delivery and nanoparticles:applications and hazards. Int J Nanomed 3:133–149
45. Santo VE, Rodrigues MT, Gomes ME (2013) Contributions and future perspectives on the use of magnetic nanoparticles as diagnostic and therapeutic tools in the field of regenerative medicine. Expert Rev Mol Diagn 13:553–566
46. Morris AS, Adamcakova-Dodd A, Lehman SE, Wongrakpanich A, Thorne PS, Larsen SC, Salem AK (2016) Amine modification of nonporous silica nanoparticles reduces inflammatory response following intratracheal instillation in murine lungs. Toxicol Lett 241:207–215
47. Peñaloza JP, Márquez-Miranda V, Cabaña-Brunod M, Reyes-Ramírez R, Llancalahuen FM, Vilos C, Maldonado-Biermann F, Velásquez LA, Fuentes JA, González-Nilo FD (2017) Intracellular trafficking and cellular uptake mechanism of PHBV nanoparticles for targeted delivery in epithelial cell lines. J Nanobiotechnol 15:1
48. Rauch J, Kolch W, Laurent S, Mahmoudi M (2013) Big signals from small particles: regulation of cell signaling pathways by nanoparticles. Chem Rev 113:3391–3406
49. Venkatachalam K, Wong C-O, Zhu MX (2015) The role of TRPMLs in endolysosomal trafficking and function. Cell Calcium 58:48–56
50. Wong C-O, Gregory S, Hu H, Chao Y, Sepúlveda VE, He Y, Li-Kroeger D, Goldman WE, Bellen HJ, Venkatachalam K (2017) Lysosomal degradation is required for sustained phagocytosis of bacteria by macrophages. Cell Host Microbe 21(719–730):e716
51. Anding AL, Baehrecke EH (2017) Cleaning house: selective autophagy of organelles. Dev Cell 41:10–22
52. Johnston HJ, Semmler-Behnke M, Brown DM, Kreyling W, Tran L, Stone V (2010) Evaluating the uptake and intracellular fate of polystyrene nanoparticles by primary and hepatocyte cell lines in vitro. Toxicol Appl Pharmacol 242:66–78
53. Moridikia A, Mirzaei H (2018) MicroRNAs: Potential candidates for diagnosis and treatment of colorectal cancer. J Cell Physiol 233:901–913
54. Salarinia R, Sahebkar A, Peyvandi M, Mirzaei HR, Jaafari MR, Riahi MM, Ebrahimnejad H, Nahand JS, Hadjati J, Asrami MO, Fadaei S, Salehi R, Mirzaei H (2016) Epi-Drugs and Epi-miRs: moving beyond current cancer therapies. Curr Cancer Drug Targets 16:773–788
55. Mirzaei H, Momeni F, Saadatpour L, Sahebkar A, Goodarzi M, Masoudifar A, Kouhpayeh S, Salehi H, Mirzaei HR, Jaafari MR (2018) MicroRNA: relevance to stroke diagnosis, prognosis, and therapy. J Cell Physiol 233:856–865
56. Gholamin S, Pasdar A, Khorrami MS, Mirzaei H, Mirzaei HR, Salehi R, Ferns GA, Ghayour-Mobarhan M, Avan A (2016) The potential for circulating microRNAs in the diagnosis of myocardial infarction: a novel approach to disease diagnosis and treatment. Curr Pharm Des 22:397–403
57. Mohammadi M, Goodarzi M, Jaafari MR, Mirzaei HR, Mirzaei H (2016) Circulating microRNA: a new candidate for diagnostic biomarker in neuroblastoma. Cancer Gene Ther 23:371–372
58. Khani P, Nasri F, Khani Chamani F, Saeidi F, Sadri Nahand J, Tabibkhooei A, Mirzaei H (2019) Genetic and epigenetic contribution to astrocytic gliomas pathogenesis. J Neurochem 148:188–203
59. Szuts EZ, Harosi FI (1991) Solubility of retinoids in water. Arch Biochem Biophys 287:297–304
60. Agrawal S, Zhao Q (1998) Antisense therapeutics. Curr Opin Chem Biol 2:519–528
61. Ha SW, Weitzmann MN, Beck GR Jr (2014) Bioactive silica nanoparticles promote osteoblast differentiation through stimulation of autophagy and direct association with LC3 and p62. ACS Nano 8:5898–5910
62. Chen YS, Hsiue GH (2013) Directing neural differentiation of mesenchymal stem cells by carboxylated multiwalled carbon nanotubes. Biomaterials 34:4936–4944
63. Yi C, Liu D, Fong CC, Zhang J, Yang M (2010) Gold nanoparticles promote osteogenic differentiation of mesenchymal stem cells through p38 MAPK pathway. ACS Nano 4:6439–6448
64. Yang D, Li T, Xu M, Gao F, Yang J, Yang Z, Le W (2014) Graphene oxide promotes the differentiation of mouse embryonic stem cells to dopamine neurons. Nanomedicine (London, England) 9:2445–2455
65. Zhang R, Lee P, Lui VC, Chen Y, Liu X, Lok CN, To M, Yeung KW, Wong KK (2015) Silver nanoparticles promote osteogenesis of mesenchymal stem cells and improve bone fracture healing in osteogenesis mechanism mouse model. Nanomed Nanotechnol Biol Med 11:1949–1959
66. Ilie I, Ilie R, Mocan T, Bartos D, Mocan L (2012) Influence of nanomaterials on stem cell differentiation: designing an appropriate nanobiointerface. Int J Nanomed 7:2211–2225
67. Zhao F, Zhao Y, Liu Y, Chang X, Chen C, Zhao Y (2011) Cellular uptake, intracellular trafficking, and cytotoxicity of nanomaterials. Small 7:1322–1337
68. Ko WK, Heo DN, Moon HJ, Lee SJ, Bae MS, Lee JB, Sun IC, Jeon HB, Park HK, Kwon IK (2015) The effect of gold nanoparticle size on osteogenic differentiation of adipose-derived stem cells. J Colloid Interface Sci 438:68–76
69. Li J, Li JJ, Zhang J, Wang X, Kawazoe N, Chen G (2016) Gold nanoparticle size and shape influence on osteogenesis of mesenchymal stem cells. Nanoscale 8:7992–8007
70. Lv L, Liu Y, Zhang P, Zhang X, Liu J, Chen T, Su P, Li H, Zhou Y (2015) The nanoscale geometry of TiO2 nanotubes influences the osteogenic differentiation of human adipose-derived stem cells by modulating H3K4 trimethylation. Biomaterials 39:193–205
71. Rivera-Gil P, Jimenez de Aberasturi D, Wulf V, Pelaz B, del Pino P, Zhao Y, de la Fuente JM, Ruiz de Larramendi I, Rojo T, Liang XJ, Parak WJ (2013) The challenge to relate the physicochemical properties of colloidal nanoparticles to their cytotoxicity. Acc Chem Res 46:743–749
72. Chithrani BD, Ghazani AA, Chan WC (2006) Determining the size and shape dependence of gold nanoparticle uptake into mammalian cells. Nano Lett 6:662–668
73. Seong JM, Kim BC, Park JH, Kwon IK, Mantalaris A, Hwang YS (2010) Stem cells in bone tissue engineering. Biomed Mater (Bristol, England) 5:062001
74. Li JJ, Kawazoe N, Chen G (2015) Gold nanoparticles with different charge and moiety induce differential cell response on mesenchymal stem cell osteogenesis. Biomaterials 54:226–236
75. Choi SY, Song MS, Ryu PD, Lam AT, Joo SW, Lee SY (2015) Gold nanoparticles promote osteogenic differentiation in human adipose-derived mesenchymal stem cells through the Wnt/beta-catenin signaling pathway. Int J Nanomed 10:4383–4392
76. Ferreira L (2009) Nanoparticles as tools to study and control stem cells. J Cell Biochem 108:746–752
77. Zavan B, Vindigni V, Vezzu K, Zorzato G, Luni C, Abatangelo G, Elvassore N, Cortivo R (2009) Hyaluronan based porous

nano-particles enriched with growth factors for the treatment of ulcers: a placebo-controlled study. J Mater Sci: Mater Med 20:235–247
78. Lundqvist M, Stigler J, Elia G, Lynch I, Cedervall T, Dawson KA (2008) Nanoparticle size and surface properties determine the protein corona with possible implications for biological impacts. Proc Natl Acad Sci USA 105:14265–14270
79. Mintzer MA, Simanek EE (2009) Nonviral vectors for gene delivery. Chem Rev 109:259–302
80. Pulavendran S, Rose C, Mandal AB (2011) Hepatocyte growth factor incorporated chitosan nanoparticles augment the differentiation of stem cell into hepatocytes for the recovery of liver cirrhosis in mice. J Nanobiotechnol 9:15
81. Cui ZK, Fan J, Kim S, Bezouglaia O, Fartash A, Wu BM, Aghaloo T, Lee M (2015) Delivery of siRNA via cationic Sterosomes to enhance osteogenic differentiation of mesenchymal stem cells. J Controll Release 217:42–52
82. Maia J, Santos T, Aday S, Agasse F, Cortes L, Malva JO, Bernardino L, Ferreira L (2011) Controlling the neuronal differentiation of stem cells by the intracellular delivery of retinoic acid-loaded nanoparticles. ACS Nano 5:97–106
83. Mirzaei H, Ferns GA, Avan A, Mobarhan MG (2017) Cytokines and MicroRNA in coronary artery disease. Adv Clin Chem 82:47–70
84. Keshavarzi M, Sorayayi S, Jafar Rezaei M, Mohammadi M, Ghaderi A, Rostamzadeh A, Masoudifar A, Mirzaei H (2017) MicroRNAs-based imaging techniques in cancer diagnosis and therapy. J Cell Biochem 118:4121–4128
85. Simonian M, Mosallayi M, Mirzaei H (2018) Circulating miR-21 as novel biomarker in gastric cancer: diagnostic and prognostic biomarker. J Cancer Res Ther 14:475
86. Tavakolizadeh J, Roshanaei K, Salmaninejad A, Yari R, Nahand JS, Sarkarizi HK, Mousavi SM, Salarinia R, Rahmati M, Mousavi SF, Mokhtari R, Mirzaei H (2018) MicroRNAs and exosomes in depression: potential diagnostic biomarkers. J Cell Biochem 119:3783–3797
87. Mirzaei H, Yazdi F, Salehi R, Mirzaei HR (2016) SiRNA and epigenetic aberrations in ovarian cancer. J Cancer Res Ther 12:498–508
88. Mirzaei H, Fathullahzadeh S, Khanmohammadi R, Darijani M, Momeni F, Masoudifar A, Goodarzi M, Mardanshah O, Stenvang J, Jaafari MR, Mirzaei HR (2018) State of the art in microRNA as diagnostic and therapeutic biomarkers in chronic lymphocytic leukemia. J Cell Physiol 233:888–900
89. Mirzaei H, Masoudifar A, Sahebkar A, Zare N, Sadri Nahand J, Rashidi B, Mehrabian E, Mohammadi M, Mirzaei HR, Jaafari MR (2018) MicroRNA: a novel target of curcumin in cancer therapy. J Cell Physiol 233:3004–3015
90. Saeedi Borujeni MJ, Esfandiary E, Taheripak G, Codoner-Franch P, Alonso-Iglesias E, Mirzaei H (2018) Molecular aspects of diabetes mellitus: resistin, microRNA, and exosome. J Cell Biochem 119:1257–1272
91. Jafari SH, Saadatpour Z, Salmaninejad A, Momeni F, Mokhtari M, Nahand JS, Rahmati M, Mirzaei H (2018) Breast cancer diagnosis: Imaging techniques and biochemical markers. J Cell Physiol 233:5200–5213
92. Rashidi B, Hoseini Z, Sahebkar A, Mirzaei H (2017) Anti-atherosclerotic effects of vitamins D and E in suppression of atherogenesis. J Cell Physiol 232:2968–2976
93. Mirzaei H (2017) Stroke in women: risk factors and clinical biomarkers. J Cell Biochem 118:4191–4202
94. Banikazemi Z, Haji HA, Mohammadi M, Taheripak G, Iranifar E, Poursadeghiyan M, Moridikia A, Rashidi B, Taghizadeh M, Mirzaei H (2018) Diet and cancer prevention: dietary compounds, dietary MicroRNAs, and dietary exosomes. J Cell Biochem 119:185–196
95. Hoseini Z, Sepahvand F, Rashidi B, Sahebkar A, Masoudifar A, Mirzaei H (2018) NLRP3 inflammasome: its regulation and involvement in atherosclerosis. J Cell Physiol 233:2116–2132
96. Masoudi MS, Mehrabian E, Mirzaei H (2018) MiR-21: a key player in glioblastoma pathogenesis. J Cell Biochem 119:1285–1290
97. Golabchi K, Soleimani-Jelodar R, Aghadoost N, Momeni F, Moridikia A, Nahand JS, Masoudifar A, Razmjoo H, Mirzaei H (2018) MicroRNAs in retinoblastoma: potential diagnostic and therapeutic biomarkers. J Cell Physiol 233:3016–3023
98. Mashreghi M, Azarpara H, Bazaz MR, Jafari A, Masoudifar A, Mirzaei H (2018) Angiogenesis biomarkers and their targeting ligands as potential targets for tumor angiogenesis. J Cell Physiol 233:2949–2965
99. Nahand JS, Taghizadeh-Boroujeni S, Karimzadeh M, Borran S, Pourhanifeh MH, Moghoofei M, Bokharaei-Salim F, Karampoor S, Jafari A, Asemi Z, Tbibzadeh A, Namdar A, Mirzaei H (2019) microRNAs: New prognostic, diagnostic, and therapeutic biomarkers in cervical cancer. J Cell Physiol 234:17064–17099
100. Aghdam AM, Amiri A, Salarinia R, Masoudifar A, Ghasemi F, Mirzaei H (2019) MicroRNAs as diagnostic, prognostic, and therapeutic biomarkers in prostate cancer. Crit Rev Eukaryot Gene Expr 29:127–139
101. Shabaninejad Z, Yousefi F, Movahedpour A, Ghasemi Y, Dokanehiifard S, Rezaei S, Aryan R, Savardashtaki A, Mirzaei H (2019) Electrochemical-based biosensors for microRNA detection: nanotechnology comes into view. Anal Biochem 581:113349
102. Jamali L, Tofigh R, Tutunchi S, Panahi G, Borhani F, Akhavan S, Nourmohammadi P, Ghaderian SM, Rasouli M, Mirzaei H (2018) Circulating microRNAs as diagnostic and therapeutic biomarkers in gastric and esophageal cancers. J Cell Physiol 233:8538–8550
103. Ferreira R, Fonseca MC, Santos T, Sargento-Freitas J, Tjeng R, Paiva F, Castelo-Branco M, Ferreira LS, Bernardino L (2016) Retinoic acid-loaded polymeric nanoparticles enhance vascular regulation of neural stem cell survival and differentiation after ischaemia. Nanoscale 8:8126–8137
104. Chen X, Gu S, Chen BF, Shen WL, Yin Z, Xu GW, Hu JJ, Zhu T, Li G, Wan C, Ouyang HW, Lee TL, Chan WY (2015) Nanoparticle delivery of stable miR-199a-5p agomir improves the osteogenesis of human mesenchymal stem cells via the HIF1a pathway. Biomaterials 53:239–250
105. Khanna P, Ong C, Bay BH, Baeg GH (2015) Nanotoxicity: an Interplay of Oxidative Stress, Inflammation and Cell Death. Nanomaterials (Basel, Switzerland) 5:1163–1180
106. Qureshi AT, Monroe WT, Dasa V, Gimble JM, Hayes DJ (2013) miR-148b-nanoparticle conjugates for light mediated osteogenesis of human adipose stromal/stem cells. Biomaterials 34:7799–7810
107. Ren M, Han Z, Li J, Feng G, Ouyang S (2015) Ascorbic acid delivered by mesoporous silica nanoparticles induces the differentiation of human embryonic stem cells into cardiomyocytes. Mater Sci Eng C 56:348–355
108. Liu D, He X, Wang K, He C, Shi H, Jian L (2010) Biocompatible silica nanoparticles-insulin conjugates for mesenchymal stem cell adipogenic differentiation. Bioconjug Chem 21:1673–1684
109. Namgung S, Baik KY, Park J, Hong S (2011) Controlling the growth and differentiation of human mesenchymal stem cells by the arrangement of individual carbon nanotubes. ACS Nano 5:7383–7390
110. Crowder SW, Liang Y, Rath R, Park AM, Maltais S, Pintauro PN, Hofmeister W, Lim CC, Wang X, Sung HJ (2013) Poly(epsilon-caprolactone)-carbon nanotube composite scaffolds for enhanced cardiac differentiation of human mesenchymal stem cells. Nanomedicine (London, England) 8:1763–1776

111. Saraiva C, Ferreira L, Bernardino L (2016) Traceable micro-RNA-124 loaded nanoparticles as a new promising therapeutic tool for Parkinson's disease. Neurogenesis 3:e1256855
112. Gu HR, Park SC, Choi SJ, Lee JC, Kim YC, Han CJ, Kim J, Yang KY, Kim YJ, Noh GY, No SH, Jeong JH (2015) Combined treatment with silibinin and either sorafenib or gefitinib enhances their growth-inhibiting effects in hepatocellular carcinoma cells. Clin Mol Hepatol 21:49–59
113. Li X, Tzeng SY, Liu X, Tammia M, Cheng YH, Rolfe A, Sun D, Zhang N, Green JJ, Wen X, Mao HQ (2016) Nanoparticle-mediated transcriptional modification enhances neuronal differentiation of human neural stem cells following transplantation in rat brain. Biomaterials 84:157–166
114. Park SJ, Kim S, Kim SY, Jeon NL, Song JM (2017) Highly Efficient and Rapid Neural Differentiation of Mouse Embryonic Stem Cells Based on Retinoic Acid Encapsulated Porous Nanoparticle. ACS Appl Mater Interface 9:34634–34640
115. Simonovic J, Toljic B, Nikolic N, Peric M, Vujin J, Panajotovic R, Gajic R, Bekyarova E, Cataldi A, Parpura V, Milasin J (2018) Differentiation of stem cells from apical papilla into neural lineage using graphene dispersion and single walled carbon nanotubes. J Biomed Mater Res A 106:2653–2661
116. Levy I, Sher I, Corem-Salkmon E, Ziv-Polat O, Meir A, Treves AJ, Nagler A, Kalter-Leibovici O, Margel S, Rotenstreich Y (2015) Bioactive magnetic near Infra-Red fluorescent core-shell iron oxide/human serum albumin nanoparticles for controlled release of growth factors for augmentation of human mesenchymal stem cell growth and differentiation. J Nanobiotechnol 13:34
117. Stephanopoulos N, Freeman R, North HA, Sur S, Jeong SJ, Tantakitti F, Kessler JA, Stupp SI (2015) Bioactive DNA-peptide nanotubes enhance the differentiation of neural stem cells into neurons. Nano Lett 15:603–609
118. Seo HI, Cho AN, Jang J, Kim DW, Cho SW, Chung BG (2015) Thermo-responsive polymeric nanoparticles for enhancing neuronal differentiation of human induced pluripotent stem cells. Nanomed Nanotechnol Biol Med 11:1861–1869
119. Ku B, Kim JE, Chung BH, Chung BG (2013) Retinoic acid-polyethyleneimine complex nanoparticles for embryonic stem cell-derived neuronal differentiation. Langmuir 29:9857–9862
120. Zhang R, Li Y, Hu B, Lu Z, Zhang J, Zhang X (2016) Traceable nanoparticle delivery of small interfering RNA and retinoic acid with temporally release ability to control neural stem cell differentiation for Alzheimer's Disease Therapy. Adv Mater (Deerfield Beach, Fla) 28:6345–6352
121. Akhavan O, Ghaderi E (2013) Flash photo stimulation of human neural stem cells on graphene/TiO_2 heterojunction for differentiation into neurons. Nanoscale 5:10316–10326
122. Park SY, Park J, Sim SH, Sung MG, Kim KS, Hong BH, Hong S (2011) Enhanced differentiation of human neural stem cells into neurons on graphene. Adv Mater (Deerfield Beach, Fla) 23:H263–H267
123. Guo W, Wang S, Yu X, Qiu J, Li J, Tang W, Li Z, Mou X, Liu H, Wang Z (2016) Construction of a 3D rGO-collagen hybrid scaffold for enhancement of the neural differentiation of mesenchymal stem cells. Nanoscale 8:1897–1904
124. Glaser T, Bueno VB, Cornejo DR, Petri DF, Ulrich H (2015) Neuronal adhesion, proliferation and differentiation of embryonic stem cells on hybrid scaffolds made of xanthan and magnetite nanoparticles. Biomed Mater (Bristol, England) 10:045002
125. Bostancioglu RB, Gurbuz M, Akyurekli AG, Dogan A, Koparal AS, Koparal AT (2017) Adhesion profile and differentiation capacity of human adipose tissue derived mesenchymal stem cells grown on metal ion (Zn, Ag and Cu) doped hydroxyapatite nano-coated surfaces. Colloids Surf B 155:415–428
126. Qin H, Zhu C, An Z, Jiang Y, Zhao Y, Wang J, Liu X, Hui B, Zhang X, Wang Y (2014) Silver nanoparticles promote osteogenic differentiation of human urine-derived stem cells at noncytotoxic concentrations. Int J Nanomed 9:2469–2478
127. Wang Q, Chen B, Cao M, Sun J, Wu H, Zhao P, Xing J, Yang Y, Zhang X, Ji M, Gu N (2016) Response of MAPK pathway to iron oxide nanoparticles in vitro treatment promotes osteogenic differentiation of hBMSCs. Biomaterials 86:11–20
128. Wu G, Feng C, Hui G, Wang Z, Tan J, Luo L, Xue P, Wang Q, Chen X (2016) Improving the osteogenesis of rat mesenchymal stem cells by chitosan-based-microRNA nanoparticles. Carbohyd Polym 138:49–58
129. Logan N, Sherif A, Cross AJ, Collins SN, Traynor A, Bozec L, Parkin IP, Brett P (2015) TiO2-coated CoCrMo: improving the osteogenic differentiation and adhesion of mesenchymal stem cells in vitro. J Biomed Mater Res, Part A 103:1208–1217
130. Nayak TR, Andersen H, Makam VS, Khaw C, Bae S, Xu X, Ee PL, Ahn JH, Hong BH, Pastorin G, Ozyilmaz B (2011) Graphene for controlled and accelerated osteogenic differentiation of human mesenchymal stem cells. ACS Nano 5:4670–4678
131. Luo Y, Shen H, Fang Y, Cao Y, Huang J, Zhang M, Dai J, Shi X, Zhang Z (2015) Enhanced proliferation and osteogenic differentiation of mesenchymal stem cells on graphene oxide-incorporated electrospun poly(lactic-co-glycolic acid) nanofibrous mats. ACS Appl Mater Interfaces 7:6331–6339
132. Akhavan O, Ghaderi E, Shahsavar M (2013) Graphene nanogrids for selective and fast osteogenic differentiation of human mesenchymal stem cells. Carbon 59:200–211
133. Nayak TR, Jian L, Phua LC, Ho HK, Ren Y, Pastorin G (2010) Thin films of functionalized multiwalled carbon nanotubes as suitable scaffold materials for stem cells proliferation and bone formation. ACS Nano 4:7717–7725
134. Ravichandran R, Venugopal JR, Sundarrajan S, Mukherjee S, Ramakrishna S (2012) Precipitation of nanohydroxyapatite on PLLA/PBLG/Collagen nanofibrous structures for the differentiation of adipose derived stem cells to osteogenic lineage. Biomaterials 33:846–855
135. Qiu J, Li D, Mou X, Li J, Guo W, Wang S, Yu X, Ma B, Zhang S, Tang W, Sang Y, Gil PR, Liu H (2016) Effects of Graphene Quantum dots on the self-renewal and differentiation of mesenchymal stem cells. Adv Healthcare Mater 5:702–710
136. Sridhar S, Venugopal JR, Sridhar R, Ramakrishna S (2015) Cardiogenic differentiation of mesenchymal stem cells with gold nanoparticle loaded functionalized nanofibers. Colloids Surf B 134:346–354
137. Ravichandran R, Sridhar R, Venugopal JR, Sundarrajan S, Mukherjee S, Ramakrishna S (2014) Gold nanoparticle loaded hybrid nanofibers for cardiogenic differentiation of stem cells for infarcted myocardium regeneration. Macromol Biosci 14:515–525
138. Xue D, Zheng Q, Zong C, Li Q, Li H, Qian S, Zhang B, Yu L, Pan Z (2010) Osteochondral repair using porous poly(lactide-co-glycolide)/nano-hydroxyapatite hybrid scaffolds with undifferentiated mesenchymal stem cells in a rat model. J Biomed Mater Res Part A 94:259–270
139. Wise JK, Yarin AL, Megaridis CM, Cho M (2009) Chondrogenic differentiation of human mesenchymal stem cells on oriented nanofibrous scaffolds: engineering the superficial zone of articular cartilage. Tissue Eng Part A 15:913–921
140. Spadaccio C, Rainer A, Trombetta M, Vadalá G, Chello M, Covino E, Denaro V, Toyoda Y, Genovese JA (2009) Poly-L-lactic acid/hydroxyapatite electrospun nanocomposites induce chondrogenic differentiation of human MSC. Ann Biomed Eng 37:1376–1389
141. Lee JH, Shim W, Choolakadavil Khalid N, Kang WS, Lee M, Kim HS, Choi J, Lee G, Kim JH (2015) Random networks of single-walled carbon nanotubes promote mesenchymal stem

cell's proliferation and differentiation. ACS Appl Mater Interfaces 7:1560–1567
142. Chen W, Tsai PH, Hung Y, Chiou SH, Mou CY (2013) Nonviral cell labeling and differentiation agent for induced pluripotent stem cells based on mesoporous silica nanoparticles. ACS Nano 7:8423–8440
143. Holmes B, Fang X, Zarate A, Keidar M, Zhang LG (2016) Enhanced human bone marrow mesenchymal stem cell chondrogenic differentiation in electrospun constructs with carbon nanomaterials. Carbon 97:1–13
144. Norizadeh-Abbariki T, Mashinchian O, Shokrgozar MA, Haghighipour N, Sen T, Mahmoudi M (2014) Superparamagnetic nanoparticles direct differentiation of embryonic stem cells into skeletal muscle cells. J Biomater Tissue Eng 4:579–585
145. Saraiva C, Praca C, Ferreira R, Santos T, Ferreira L, Bernardino L (2016) Nanoparticle-mediated brain drug delivery: overcoming blood-brain barrier to treat neurodegenerative diseases. J Control Release 235:34–47
146. Cao P, Mooney R, Tirughana R, Abidi W, Aramburo S, Flores L, Gilchrist M, Nwokafor U, Haber T, Tiet P, Annala AJ, Han E, Dellinger T, Aboody KS, Berlin JM (2017) Intraperitoneal administration of neural stem cell-nanoparticle conjugates targets chemotherapy to ovarian tumors. Bioconjug Chem 28:1767–1776
147. Guimard NK, Gomez N, Schmidt CE (2007) Conducting polymers in biomedical engineering. Prog Polym Sci 32:876–921
148. Park SY, Park J, Sim SH, Sung MG, Kim KS, Hong BH, Hong S (2011) Enhanced differentiation of human neural stem cells into neurons on graphene. Adv Mater 23:H263–H267
149. Defteralı Ç, Verdejo R, Majeed S, Boschetti-de-Fierro A, Méndez-Gómez HR, Díaz-Guerra E, Fierro D, Buhr K, Abetz C, Martínez-Murillo R (2016) In vitro evaluation of biocompatibility of uncoated thermally reduced graphene and carbon nanotube-loaded PVDF membranes with adult neural stem cell-derived neurons and glia. Front Bioeng Biotechnol 4:94
150. Santos T, Ferreira R, Maia J, Agasse F, Xapelli S, Ls Cortes, Bragança J, Malva JO, Ferreira L, Bernardino L (2012) Polymeric nanoparticles to control the differentiation of neural stem cells in the subventricular zone of the brain. ACS Nano 6:10463–10474
151. Baranes K, Shevach M, Shefi O, Dvir T (2015) Gold nanoparticle-decorated scaffolds promote neuronal differentiation and maturation. Nano Lett 16:2916–2920
152. He W, Bellamkonda RV (2005) Nanoscale neuro-integrative coatings for neural implants. Biomaterials 26:2983–2990
153. Chao T-I, Xiang S, Chen C-S, Chin W-C, Nelson A, Wang C, Lu J (2009) Carbon nanotubes promote neuron differentiation from human embryonic stem cells. Biochem Biophys Res Commun 384:426–430
154. Chao TI, Xiang S, Lipstate JF, Wang C, Lu J (2010) Poly (methacrylic acid)-grafted carbon nanotube scaffolds enhance differentiation of hESCs into neuronal cells. Adv Mater 22:3542–3547
155. Sridharan I, Kim T, Wang R (2009) Adapting collagen/CNT matrix in directing hESC differentiation. Biochem Biophys Res Commun 381:508–512
156. Chen W, Tsai P-H, Hung Y, Chiou S-H, Mou C-Y (2013) Nonviral cell labeling and differentiation agent for induced pluripotent stem cells based on mesoporous silica nanoparticles. ACS Nano 7:8423–8440
157. Chen G-Y, Pang D-P, Hwang S-M, Tuan H-Y, Hu Y-C (2012) A graphene-based platform for induced pluripotent stem cells culture and differentiation. Biomaterials 33:418–427
158. Chung C-Y, Yang J-T, Kuo Y-C (2013) Polybutylcyanoacrylate nanoparticle-mediated neurotrophin-3 gene delivery for differentiating iPS cells into neurons. Biomaterials 34:5562–5570