CHAPTER 8

Nanoparticulate systems for monitoring of therapeutic cells

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A significant cause of worldwide morbidity and mortality that carries a heavy health care burden is cardiovascular disease. The mortality rate of cardiovascular disease, which is considered the leading cause of death in the United States, is close to 801,000 people every year [1, 2]. Coronary heart disease, deep vein thrombosis, myocardial infarction (MI), and pulmonary embolism are some of the many examples of cardiovascular diseases. They all lead to ischemia and tissue death. Among them, important conditions that cause mortality are MI and heart failure. Technological innovations and novel therapies are necessary to counter these diseases given the bleak outcomes. Advances in research tools and treatments can be achieved through the synergy of biology and nanotechnology [3–5]. Nanoparticles (NPs) for drug delivery and therapeutic stem cells (SCs) are specific examples of nanobiotechnology in action [6–8]. Aside from drug delivery, nanotechnology can be utilized for other therapeutic purposes in treating cardiovascular diseases. SC therapy, which has the capacity to improve repair of cardiac tissue, is an example [9–11].

Stem cell therapy for cardiac repair

Typically regarded as a postmitotic organ, the adult heart has not been known to have high potential for self-renewal. A change in this belief occurred not long ago [12]. There has been growing interest lately in SC therapy, which is a promising technique to regenerate tissue, for repairing cardiac tissue in ischemic heart disease [13]. SC therapy has been demonstrated to be an attractive therapeutic strategy for treating cardiovascular disease based on the results of many clinical trials. Since SCs were initially

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transplanted into human patients, various kinds have been employed, such as SCs derived from bone marrow, cardiac progenitors, and embryonic stem cells (ESCs) and their derivatives [14].

Potential mechanisms of adult SCs in cardiovascular regeneration

Direct and indirect/paracrine mechanisms influence the ability of SCs to regenerate injured tissue (Fig. 1). Injecting SCs that directly differentiate and integrate into the myocardium to offset the loss of endothelial cells or cardiomyocytes is an example of a direct mechanism [14]. A highly attractive therapy for injured myocardial tissue is cell transplantation. Treating heart failure with bone marrow-derived mesenchymal stromal cells (BMSCs) has been extensively examined in animal and clinical investigations. Treating MI with induced pluripotent stem cells (iPSCs) and ESCs has recently shown immense potential.

Different kinds of stem cells for heart treatment:

(1) *Mesenchymal stem cells (MSCs)*: Friedenstein et al. discovered MSCs [15]. Different mesodermal lineages, including adipocytes, chondrocytes, and osteocytes, may arise from the differentiation of MSCs, which are heterogeneous populations of fibroblast-like multipotent cells. While initially derived from bone marrow, MSCs can be located in numerous other tissues as well. Some examples include muscle and adipose tissue, placenta, and umbilical cord [16]. For treating cardiac injury, the most commonly employed SCs are MSCs, because they can be obtained easily from various tissues and altered easily by viral vectors [17].

(2) *Adipose tissue-derived stem cells (ADSCs)*: A straightforward surgical operation can be performed to obtain ADSCs from subcutaneous adipose tissues. The procedure is less costly and invasive than collagenase digestion and acquisition of cells from the bone marrow [18].

(3) *Embryonic stem cells (ESCs)*: The inner cell mass of blastocysts contains ESCs which are multipotent cells with unlimited self-renewal ability and can differentiate into cells from the three germ layers (ectoderm, mesoderm, and endoderm) [19].

(4) *Induced pluripotent stem cells (iPSCs)*: For treating cardiac diseases, another source of SCs is the iPSC. The initial production of iPSCs involved somatic cells which were co-transferred with the c-Myc, Klf4 and Oct-4, and Sox-2 transcription factors [20].

(5) *Endothelial progenitor cells (EPCs)*: A heterogeneous cell population, the EPC can be present in peripheral blood at various stages of endothelial differentiation or arise in the bone marrow from hybrid progenitor cells. Since numerous surface markers are the same between EPCs and ECs or hematopoietic SCs, they are hard to tell apart [21].

(6) *Cardiac stem cells (CSCs)*: While CSCs have been derived from cardiac tissue and undergone in vitro expansion for in vivo cardiac therapy, their source is yet unknown [14].

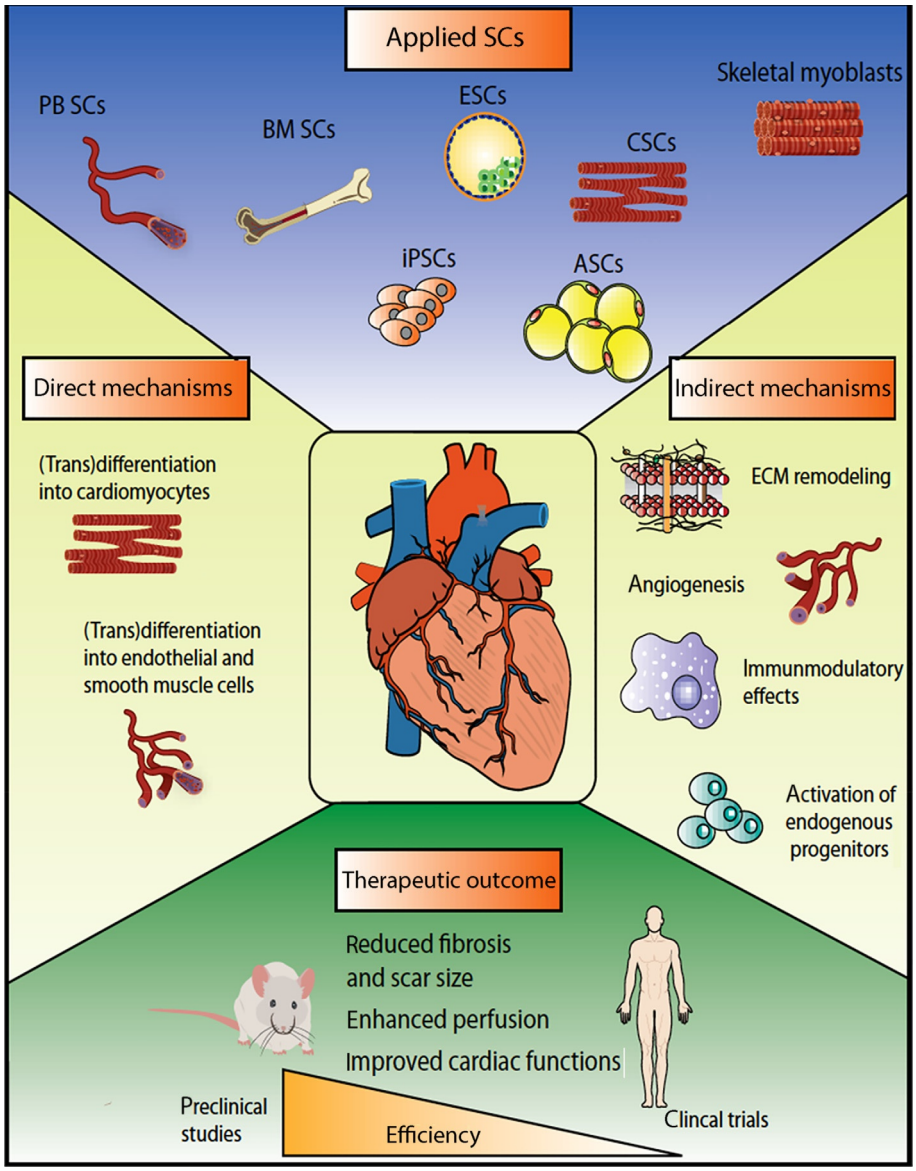

Fig. 1 Cardiac regeneration using stem cell (SC) therapy. To encourage cardiac regeneration of the adult heart, preclinical and clinical investigations have examined multipotent adult SCs from different tissues (adipose, cardiac, bone marrow (BM), and peripheral blood (PB)), pluripotent SCs (induced pluripotent SC (iPSCs), embryonic SC (ESCs)), and skeletal myoblasts. Regeneration is promoted by the differentiation of SCs into cardiomyocytes, endothelial, and smooth muscle cells. Favorable outcomes of SC therapy were determined to be mediated primarily by indirect paracrine mechanisms based on many in vitro and in vivo results. Extracellular matrix (ECM) remodeling in the damaged tissue is positively affected by the release of soluble factors. Paracrine signaling of SCs likewise promotes immunomodulatory effects and the emergence of new blood vessels. A major therapeutic effect of SC therapy was observed in many preclinical investigations. Examples include increased cardiac performance, decreased fibrosis and size of infarction, and improved perfusion. On the other hand, clinical trials reported mixed results regarding function. The notable advantages of SC therapy seen in different animal studies were not corroborated. *ASC*, adipose-derived stromal/stem cells; *CSC*, cardiac SC.

Stem cell and NP integration

Given the exceptional chemical and physical properties of NPs, they have been extensively employed in conjunction with SC therapy [22, 23]. It is possible to genetically engineer SCs with the assistance of NPs to augment the paracrine profile. SCs can be labeled with NPs and monitored in vivo under several imaging modalities to enhance knowledge of the SCs' behaviors and fate in myocardium damaged by ischemia. In addition, the retention of SCs in myocardium can be improved using NPs [24]. As a result of these new insights, there have been increased attempts to create smarter multifunctional NPs for practical use in cells. Enhancing SCs may help the repairing of cardiac tissue. Beneficial cells for therapeutic applications include differentiated cells (e.g., cells in the immune system) and human primary cells such as adult SCs [25].

NPs for genetic engineering in stem cells

Using viral vectors for the delivery of different therapeutic genes (e.g., antiapoptotic and proangiogenic genes) has been performed to create SCs which are genetically engineered to repair cardiac tissue [26, 27]. The design and fabrication of complex nanostructured vehicles for various kinds of NPs have been accomplished within the past 10 years for transporting into somatic cells therapeutic genes [3, 28]. Genetically engineered SCs established using NPs have been examined as well and demonstrated tremendous potential for repairing tissues [29]. NPs are more biocompatible in cells and tissues than viral vectors. The advantages of NP-based vectors over their viral counterparts may become apparent in future clinical trials given the considerable attempts made to increase the efficacy of gene delivery.

Liposomes are among the foremost examples in this field. Liposomes, which are composed of aqueous inner cavities and lamellar phase lipid bilayers, are spherical particles [30]. Employed for gene delivery into SCs, liposomes with 100 nm in mean diameter are considered NPs. Therapeutic genes including DNA or RNA may be attached to the surface of liposomes or enclosed in the interior aqueous phase. Genes are protected from deterioration and nonspecific binding during transfection by these "lipoplexes," which are the liposome/gene complexes [31].

Many types of polymer-based NPs, including chitosan, dendrimers, and polyethylenimine (PEI), have been synthesized and utilized as gene vectors in the past 10 years. Condensed "polyplexes" are established from the interaction between negatively charged genes and their dense positively charged groups, which are frequently primary amines [32]. Usually particles with positive charges, polyplexes can attach to anionic sites on cell membranes and be taken up by cells afterwards. Genes are protected from being degraded by cationic polymers, which also help them escape from endosomes and

lysosomes. To enhance their transgene capability (e.g., achieve precise targeting, decrease cytotoxicity, improve efficiency), surface modification of polymers can be done easily [24, 33, 34].

A new and promising kind of gene vector is the inorganic NP [35]. Because genes can be loaded into inorganic NPs by absorption or conjugation and subsequently taken up by cells, inorganic NPs can be mixed with organic materials to carry out the transfer of genes or used alone. The development of various kinds of inorganic NPs (e.g., calcium phosphate, carbon nanotubes, gold, magnetic nanobeads, quantum dots, and silica) for delivering genes into SCs has been achieved [22]. Inorganic NPs are preferable for their low cytotoxicity and ease of synthesis, even though their transfection efficiencies in the majority of cell lineages are modest [35, 36].

Stem cell targeting

Assessing how transplanted SCs differentiate, migrate, and survive in myocardium, along with pinpointing their mechanisms, is of high importance. In the past decade, the emergence of direct and indirect SC labeling methods has contributed toward realizing this goal. SCs can be transfected with reporter genes which are overexpressed using indirect labeling. SCs are incubated with labeling agents in the direct labeling technique [37]. Their ability to be functionally modified, biocompatible, and detected in real-time makes NPs strong direct labeling agents [38]. SCs that are transplanted into myocardium can be monitored using NPs as labeling agents. The mechanisms of endocytosis for NP gene vectors and NP labeling agents may be identical. NP labeling agents have magnetic and optical properties and may be directly detected ex vivo.

The ability of magnetic resonance imaging (MRI) to detect cell signals and provide two- or three-dimensional imaging of cardiac tissue may be used in conjunction with superparamagnetic iron oxide (SPIO) NPs as SC labeling agents for repairing cardiac tissue [39–41]. As demonstrated in recent clinical investigations on acute myocardial infarction (AMI) and atherosclerosis, the area of cardiovascular MRI with contrast enhancement may be advanced with IONs. Novel research directions including remote magnetic drug targeting (MDT) are also made possible by IONs. The rates of relaxation of water protons in tissues that are close by can be altered by magnetic NPs. This allows for clear images of NPs on MRI which have been enhanced with contrast [42–44].

MRI tracking

Imaging methods used in medical applications include MRI, positron emission tomography (PET), single-photon emission computed tomography (SPECT), ultrasound, and X-ray computed tomography (CT) [45–48]. While high-resolution images can be

produced by MRI and CT, PET and SPECT have low-resolution and high sensitivity. MRI, which can examine immune cell morphology and function, is the most flexible and sensitive technique among these approaches. Magnetic NPs can be utilized for tracking cells by MRI. Various contrast agents are used in MRI. The acceleration of magnetic relaxation by contrast agents helps to increase the contrast at regions of interest [49–51]. The capacity of NP contrast agents for carrying as many as hundreds of thousands of imaging moieties in each structure is the most significant characteristic [52].

A major NP-based MRI contrast agent is the SPIO NP [53–55]. SCs can be labeled with SPIO NPs in myocardium without effects on the cells' ability to differentiate, migrate, proliferate, and be viable [56, 57]. However, the survival rate of SPIO-labeled SCs may be overestimated by MRI according to some studies. Furthermore, they could not be tracked for a prolonged period of time by MRI. SPIO NPs released from dead SCs are gradually phagocytosed by macrophages within the myocardium and lead to incorrect hypointensity on MRI [58]. The role of assisting and evaluating SC transplants in a specific tissue region can nevertheless be achieved by SPIO NPs. Among the most popular in MRI, gadolinium (Gd) is a paramagnetic contrast agent which, in T1-weighted sequences, produces hyperintensity. A complex typically forms between the Gd^{3+} ion and a chelating ligand, including diethylenetriaminepentaacetic acid (Gd-DTPA). Gd complexes cannot easily move through cell membranes and have a comparatively low relaxation [59]. NPs can help with cell internalization and concentrate Gd in the cytoplasm for tracking SCs. Single-walled carbon nanotubes can enclose tiny clusters of Gd^{3+} ions, which can be taken up efficiently by MSCs [60]. A Gd-liposome produced from conjugating Gd with liposome NPs can mark MSCs and be monitored in vivo for a minimum of 20 days [61].

Optical tracking

Conjugation of NPs with optical agents, which may be delivered into SCs for labeling and tracking purposes ex vivo, is possible for some kinds of NPs, including carbon nanotubes, gold nanorods, and silica NPs [62, 63]. Inexpensive and effective, they allow for repeated noninvasive monitoring. However, fluorescence penetrates little into the skin (<4 cm) and becomes absorbed and scattered. Their utility is thus limited to human superficial tissues or small animals [64, 65]. Improved capability for penetrating tissues and sensitivity to detection relative to conventional optical labels have seen some new kinds of optical NPs (e.g., quantum dots and up conversion NPs). These novel NPs open the possibility for tracking SCs in human hearts [66, 67].

Multimodal tracking

Cell labeling agents should preferably offer high resolution and sensitivity regarding in vivo cell behaviors. However, no individual modality can currently satisfy all the

demands of cellular tracking. Multimodal approaches including MRI contrast agents, optical agents, and radionuclides can work together to surpass any individual modality [37, 68, 69]. NPs have immense surface areas and may undergo functional modification to include various labeling agents [38, 70]. Biology, imaging, medicine, and nanotechnology work together to optimize the hybrid properties of NPs. The ability to assess SC behavior in terms of anatomy and function using NP-based multimodal labeling agents holds enormous potential.

Stem cell retention

Treating cardiovascular diseases, such as enhancing the therapeutic effect and myocardial recovery and using gene or SC approaches, has great potential. However, the low accumulation and retention of drugs at the target site restrict the application of these techniques, even though various compounds and routes of administration have been explored. These findings undermine the translation of these approaches into clinical use [71, 72]. A threefold improvement in cardiac cell retention with a magnetic field and an increase in capillary density and cardiac performance were found in MSCs labeled with superparamagnetic oxide NPs [73].

Stem cell therapy potential

Novel SC therapies promoting the regeneration of damaged myocardium can transform the treatment of cardiovascular diseases. The repair of injured cardiac tissue and improvement of ventricular function described in a 2001 preclinical investigation quickly spurred the rise of translating SC therapies [74, 75]. MI can be treated with injectable hydrogels. Enhanced cardiac function has been shown in studies using Laplace's Law (greater wall thickness and less wall stress). Injectable hydrogels tested as therapeutics for MI include many different natural polymers (e.g., chitosan, collagen, fibrin, hyaluronic acid, keratin, and Matrigel). Outstanding biocompatibility and stimulation of cell differentiation, migration, or proliferation are characteristic of these therapeutics. In effect, heart regeneration or repair eventually ensues [76].

A novel material in SC therapy is the nanogel. Used in allogeneic/xenogeneic cell therapies, synthetic porous nanogels serve as advantageous cell carriers. In one example, regenerative factors can be released to encourage regeneration and immune cells are prevented from entering through the application of a poly(*N*-isopropylacrylamide-*co*-acrylic acid) or P(NIPAM-AA) nanogel. Functioning as a barrier and scaffold, the nanogel blocks T cells from crossing and attacking the enclosed CSCs and increases retention of cells. Promotion of endogenous regeneration and increased cardiac function are eventual outcomes of the treatment [77].

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