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Nanotechnology for mesenchymal stem cell therapies

Bruna Corradetti [a,b,*], Mauro Ferrari [b,c]

[a] Department of Life and Environmental Sciences, Università Politecnica delle Marche, Via Brecce Bianche, 60131 Ancona, Italy
[b] Department of Nanomedicine, Houston Methodist Research Institute, 6670 Bertner Ave., Houston, TX 77030, USA
[c] Department of Medicine, Weill Cornell Medical College, New York, NY 10065, USA

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ABSTRACT

Mesenchymal stem cells (MSC) display great proliferative, differentiative, chemotactic, and immune-modulatory properties required to promote tissue repair. Several clinical trials based on the use of MSC are currently underway for therapeutic purposes. The aim of this article is to examine the current trends and potential impact of nanotechnology in MSC-driven regenerative medicine. Nanoparticle-based approaches are used as powerful carrier systems for the targeted delivery of bioactive molecules to ensure MSC long-term maintenance *in vitro* and to enhance their regenerative potential. Nanostructured materials have been developed to recapitulate the stem cell niche within a tissue and to instruct MSC toward the creation of regeneration-permissive environment. Finally, the capability of MSC to migrate toward the site of injury/inflammation has allowed for the development of diagnostic imaging systems able to monitor transplanted stem cell bio-distribution, toxicity, and therapeutic effectiveness.

1. Introduction

Over the few past years, the control over stem cell fate has become a major area of interest in the field of regenerative medicine and therapeutic intervention for a diverse range of pathologies [1]. Stem cells are defined as a population of immature, non-specialized cells able to self-renew and differentiate [2,3]. They can be derived from embryonic and adult tissues and thus categorized into pluripotent and multipotent cells respectively, as their differentiation potential is tightly dependent on their origin [4]. Embryonic stem cells (ESC) are isolated from the inner mass of the blastocyst and are considered pluripotent as they give rise to all the cell lineages of the three embryonic germ layers (endoderm, ectoderm, and mesoderm) [5,6]. Adult tissues contain a population of mesenchymal stem cells (MSC), which are able to differentiate toward the mesodermal lineage (*i.e.* osteoblasts, adipocytes, and chondrocytes) [7]. Despite their greater proliferative and differentiative potential, the use of ESC for clinical applications is limited by the ethical issues associated to the embryo destruction required to derive them [8], and by their tumorigenic potential [9]. Since the first attempt to use them for regenerative purposes *in vivo* in 1950 [10,11], adult MSC have been identified as alternative therapeutic tools to help recover tissue functionality in various syndromes, including Parkinson's [12], Alzheimer's [13], cardiovascular diseases [14] and degenerative disorders affecting muscles [15], lung [16], liver [17], tendons [18] and other organs. MSC transplantation in humans is considered to be safe and several human clinical trials have been developed so far (Table 1), with no detrimental effects over a 6.8-year period [19–21].

The regenerative potential attributed to transplanted MSC is mainly due to their capability to migrate to the site of injury/inflammation/tumor (chemotaxis) and support tissue homeostasis by enhancing the nutrient supply to endogenous cells [22]. Through the release of bioactive soluble factors (lipids, gases, growth factors and cytokines), MSC are known to inhibit apoptosis and fibrosis, enhance angiogenesis, stimulate mitosis and/or differentiation of tissue-resident progenitor cells and modulate the immune response [23]. Recent findings demonstrated that paracrine factors contained in MSC conditioned media have the potential to mediate tissue protection and repair. They have been proven effective in endometrial cell replenishment when low proliferation is associated to pregnancy failure *in vitro* [24] and to be sufficient to stimulate the structural and functional regeneration of cardiac [25,26], renal [27,28], tendon [29], and spinal cord [30] tissues *in vivo*. Fig. 1 summarizes the MSC features that make them a powerful tool for therapeutic purposes.

Nanotechnology encompasses a wide spectrum of nanoscale or nanostructured (1–1000 nm) delivery systems, implants, and medical devices for imaging and diagnosis, which holds the promise to enhance stem cell research and the effectiveness of stem cell-based therapy [31].

Nanoscale materials and structures applied to stem cell field include nanoparticles [32], carbon nanotubes [33], quantum dots [34,35], nanofibers [36], and nanoscale-engineered substrates [37]. Nanotechnologies have been widely applied to cell biology, in particular to cancer research and therapy. Several hundreds of different nanomedicine-

* Corresponding author at: Department of Life and Environmental Sciences, Università Politecnica delle Marche, Via Brecce Bianche, 60131 Ancona, Italy.
E-mail address: b.corradetti@univpm.it (B. Corradetti).

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Table 1
Completed clinical trials of MSC for regenerative medicine.

Diseases	Clinical trials ID	Products	Intervention
Cartilage			
Rheumatoid arthritis	NCT01873625	Autologous BM-MSC	Transplantation
Osteoarthritis	NCT01227694, NCT00850187, NCT01207661, NCT01183728, NCT01504464, NCT01436058	Autologous BM-MSC	Articular injection, implantation w/ scaffold
Articular chondral defect	NCT01747681, NCT01586312	Autologous BM-MSC Allogeneic BM-MSC	Microfracture treatment, articular injection
Cartilage injury	NCT01041001	Allogeneic-unrelated UCB-MSC	Microfracture treatment
Bone			
Bone cyst	NCT01207193	Autologous BM-MSC	Injection
Nonunion fractures	NCT01206179		Injection in fractured zone
Adult periodontitis	NCT00221130		Transplantation
Leg length inequality	NCT01210950		Injection with platelet rich plasma
Pancreas/liver			
Critical limb ischemia diabetes	NCT01257776	Autologous AT-MSC	Intra-arterial administration through a selective cannulation of target common femoral artery
Liver cirrhosis	NCT00913289, NCT01062750, NCT01342250	Autologous AT-MSC, UCB-MSC	Liver injection, intrahepatic arterial catheterization
Wilson's disease	NCT01378182	Allogenic BM-MSC	Transplantation *via* portal vein or hepatic artery or peripheral vein
Heart			
Dilated cardiomyopathy	NCT00629096	Autologous BM-MSC	Intracoronary infusion
Heart failure	NCT00927784		Intramyocardial Injection

MSC: mesenchymal stem cell; BM: bone marrow; AT: adipose tissue; UCB: umbilical cord blood.

based products are presently in the clinical practice or in various stages of pre-clinical and clinical development worldwide [38–40]. Their use in regenerative medicine is more recent. This is probably due to: *i*) the emergent awareness on the stem cell-based therapy effectiveness (or pitfalls) and on the role stem cells play in tissue repair, *ii*) the identification of alternative stem cell lines with greater regenerative potential (*i.e.* induced pluripotent stem cells — iPSC); and *iii*) regeneration-focused advances in the development of nanomaterials successfully applied to medicine.

In regenerative medicine, cutting-edge nano-engineered tools and techniques are used as means to recapitulate the basic life processes occurring within the extracellular environment to stimulate endogenous stem cells to respond to inflammation and activate the body's self-healing machinery [41]. To accomplish this goal, understanding the dynamics of progenitor cells within a tissue is crucial as the environment the cells are exposed to highly affects their fate [42,43]. The ability to engineer materials able to mimic the function and the overall hierarchical architecture of a tissue has deepened the knowledge of several biological processes occurring during tissue homeostasis [44,45]. These processes include the molecular mechanisms activated in response to cell–matrix or cell–cell interactions, ultimately affecting stem cell adhesion, proliferation, differentiation and immune-suppressive or -modulatory potential, thus leading to an improved outcome when it comes to regenerative medicine applications.

The aim of the present review is to shed the light on some of the most innovative nanotechnologies developed to improve the therapeutic outcome of stem cell-based approaches for regenerative medicine, by mimicking the natural extracellular microenvironment [46]. Extensive studies have been published regarding the impact of nanotechnology in a broad spectrum of stem cell types, including pluripotent [47], neural [48,49], and hematopoietic [50] cell-driven tissue engineering.

In this review we restrict our focus on MSC to provide a concise and informative coverage of the current state of the art of the wide range of nanotechnologies for regenerative medicine. MSC were selected as the most characterized stem cell population for biomedical applications, especially for what pertains their interaction with micro- and nano-scale microenvironment [51], which is essential to develop physiologically functional engineered tissues.

We encompass a broad spectrum of nanotech applications including: *i*) biodegradable nanoparticle-based systems for the provision of bio-chemical, physical and genetic cues to control MSC behavior and enhance their beneficial properties, *ii*) nanostructured scaffolds and surfaces to recapitulate the stem cell niche within a tissue, and *iii*) nanoparticle encapsulation into MSC as carriers to monitor their effectiveness in

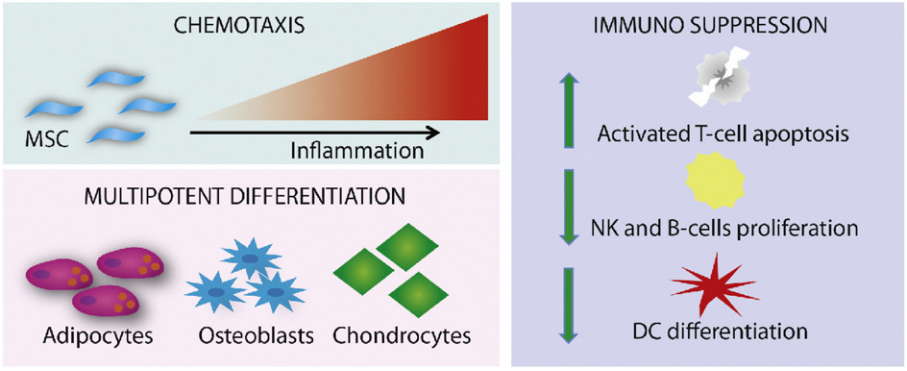

Fig. 1. Image summarizing the features that make mesenchymal stem cells (MSC): cell migration toward the site of inflammation, multipotent differentiative potential, and immunosuppression (NK: natural killers, DC: dendritic cells).