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Review Article

Mesenchymal Stem Cells: Angels or Demons?

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Mesenchymal stem cells (MSCs) have been used in cell-based therapy in various disease conditions such as graft-versus-host and heart diseases, osteogenesis imperfecta, and spinal cord injuries, and the results have been encouraging. However, as MSC therapy gains popularity among practitioners and researchers, there have been reports on the adverse effects of MSCs especially in the context of tumour modulation and malignant transformation. These cells have been found to enhance tumour growth and metastasis in some studies and have been related to anticancer-drug resistance in other instances. In addition, various studies have also reported spontaneous malignant transformation of MSCs. The mechanism of the modulatory behaviour and the tumorigenic potential of MSCs, warrant urgent exploration, and the use of MSCs in patients with cancer awaits further evaluation. However, if MSCs truly play a role in tumour modulation, they can also be potential targets of cancer treatment.

1. Introduction

Mesenchymal stem cells (MSCs) are a group of heterogeneous multipotent cells which can be isolated from many tissues throughout the body. The discovery of mesenchymal stem cells can be dated back to the 1960s [1]. In recent years, MSCs have gained popularity among stem cell researchers due to their ability to self-renew and differentiate into many different cell types particularly cells of mesodermal origin such as osteoblasts, chondrocytes, and adipocytes in culture [2–4]. MSCs have also been reported to transdifferentiate into cells of ectodermal [5] and endodermal [6, 7] origins. Besides, MSCs have been applied clinically in patients with severe dilated cardiomyopathy, cartilage disorders, stroke, and autoimmune diseases with very encouraging results [8–11]. However, despite the many potential therapeutic benefits of MSCs, the use of these cells has been reported to bring adverse effects such as an increased recurrence rate of cancer, particularly haematological malignancies. There has been increasing evidence regarding the tumour modulatory effect of MSCs, and it has been shown that MSCs may enhance tumour growth in several studies [12–14]. Besides, MSCs have also been demonstrated to undergo spontaneous malignant transformation *in vitro* [15]. This review therefore gives an overview of the benefits as well as the harmful effects of MSCs with an emphasis on the clinical implications of the use of these cells.

2. What Are Mesenchymal Stem Cells?

The discovery of MSCs can be credited to the work done by A. J. Friedenstein as early as the 1960s during which he observed that the bone marrow is a source of stem cells for mesenchymal tissues in postnatal life [16]. After harvesting bone marrow samples from the iliac crest, Friedenstein and his coworkers plated the suspension on plastic culture dishes. They observed that upon gradual removal of the haematopoeitic counterpart, there existed a population of plastic-adherent, fibroblast-like cells that could differentiate into chondrocytes and osteoblasts and named them colony-forming unit fibroblasts [1, 17]. They were later renamed mesenchymal stem cells due to their ability to differentiate into cells of mesodermal origin [18].

However, it is worth mentioning that A. J. Friedenstein was not the first to propose the existence of stem cells. Prior to his discovery of MSCs, works of several other scientists have marked important milestones in stem cell research and contributed to our current understanding of the important

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COMMENTARY

How do mesenchymal stromal cells exert their therapeutic benefit?

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In recent years mesenchymal stromal cells (MSC) have emerged as a major new form of cell therapy. While the original perception was that MSC were stem/progenitor cells with the potential to contribute to the regeneration of tissue, more recent data suggest that the principal mechanism of MSC activity is through the release of soluble mediators that elicit the observed biologic response. Future studies are needed to identify more completely the spectrum of therapeutic applications and delineate better the associated molecular and cellular mechanisms.

Mesenchymal stromal cells (MSC) are spindle-shaped, plastic-adherent cells isolated from bone marrow, adipose tissue and many other tissue sources [1,2]. Originally identified by Friedenstein *et al.* [3] as the cells of the marrow microenvironment supporting hematopoiesis, they were soon shown to differentiate into bone and have a vast potential to expand *ex vivo*. Friendenstein *et al.* [4] further showed that a subset of the cells had a high proliferative potential, generating clonal colonies when plated in tissue culture at low density, the so-called fibroblast colony-forming cells (CFU-F). Soon, it was recognized MSC could differentiate *in vitro* into fat and cartilage as well as bone. At this time, the only widely recognized stem cells were the hematopoietic stem cells. Based largely on that model, stem cells were generally defined as cells that could undergo self-renewal and differentiation into at least two lineages. As there was no clear distinction between *in vivo* and *in vitro* differentiation capacity, MSC seemed to fulfill those criteria. Owen [5] proposed the existence of stromal stem cells, analogous to the hematopoietic stem cells, that could reconstitute the hematopoietic microenvironment, and suggested the CFU-F may represent such cells. Later Caplan [6] proposed that these cells were actually MSC, with the capacity to differentiate into a wide variety of mesenchymal tissues. According to this concept, MSC could serve as a broadly applicable stem cell source for regenerative medicine, repopulating injured tissues and clinically ablated diseased tissues with healthy, terminally differentiated, tissue-specific cells [7,8].

MSC were first used clinically in the mid-1990s in a phase I trial of autologous MSC in patients undergoing autologous hematopoietic cell transplantation for breast cancer [9]. After demonstration of safety, MSC were used in a phase II trial in an effort to show that co-infusion of MSC could hasten the time for hematopoietic stem cell engraftment and hematopoietic reconstitution [10]. The proposed mechanism was based on the notion that MSC would home to the marrow space and rebuild the microenvironment.

At that time, Prockop and colleagues [11] published a seminal report demonstrating the fate of systemically infused MSC. In a murine model, gene-marked cells injected through the tail vein were identified in the marrow, spleen, bone, lung and cartilage of recipient animals. Based on the observations that MSC migrated, or perhaps homed, to bone, and that MSC could robustly differentiate to bone *in vitro*, Prockop and colleagues [12] went on to show that systemically infused MSC could engraft and contribute normal collagen to bone in a mouse model of osteogenesis imperfecta (OI). The proposed mechanism of these observations was that MSC engrafted and partially populated the host bone as differentiated

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REVIEW ARTICLE

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From the Laboratory Bench to the Patient's Bedside: An Update on Clinical Trials With Mesenchymal Stem Cells

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Mesenchymal Stem Cells (MSCs) are non-hematopoietic multi-potent stem-like cells that are capable of differentiating into both mesenchymal and non-mesenchymal lineages. In fact, in addition to bone, cartilage, fat, and myoblasts, it has been demonstrated that MSCs are capable of differentiating into neurons and astrocytes in vitro and in vivo. MSCs are of interest because they are isolated from a small aspirate of bone marrow and can be easily expanded in vitro. As such, these cells are currently being tested for their potential use in cell and gene therapy for a number of human diseases. Nevertheless, there are still some open questions about origin, multipotentiality, and anatomical localization of MSCs. In this review, we discuss clinical trials based on the use of MSCs in cardiovascular diseases, such as treatment of acute myocardial infarction, endstage ischemic heart disease, or prevention of vascular restenosis through stem cell-mediated injury repair. We analyze data from clinical trials for treatment of osteogenesis imperfecta (OI), which is a genetic disease characterized by production of defective type I collagen. We describe progress for neurological disease treatment with MSC transplants. We discuss data on amyotrophic lateral sclerosis (ALS) and on lysosomal storage diseases (Hurler syndrome and metachromatic leukodystrophy). A section of review is dedicated to ongoing clinical trials, involving MSCs in treatment of steroid refractory Graft Versus Host Disease (GVHD); periodontitis, which is a chronic disease affecting periodontium and causing destruction of attachment apparatus, heart failure, and bone fractures. Finally, we will provide information about biotech companies developing MSC therapy.

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What are Mesenchymal Stem Cells?

The microenvironment of mammalian bone marrow is composed of several different elements that support hematopoiesis and bone homeostasis (Muller-Sieburg and Deryugina, 1995; Zhang et al., 2003). It includes a heterogeneous population of cells: macrophages, fibroblasts, adipocytes, osteoprogenitors, endothelial cells (ECs), and reticular cells. Among these, there are also non-hematopoietic stem cells that posses a multilineage potential (Deans and Moseley, 2000; Bianco et al., 2001). These stem cells are commonly indicated as marrow stromal stem cells or mesenchymal stem cells (MSCs). Mesenchymal cells are primordial cells of mesodermal origin giving rise to skeletal muscle cells, blood, vascular and urogenital systems, and to connective tissues throughout the body (Prockop, 1997; Beyer Nardi and da Silva Meirelles, 2006; Sethe et al., 2006). For this reason, the word mesenchymal should be referred to stem cells that are also able to produce blood cells. In practice, however, blood cells derive from a distinct stem cell population present in bone marrow: the hemapoietic stem cells (HSCs) (Prockop, 1997; Beyer Nardi and da Silva Meirelles, 2006; Sethe et al., 2006).

MSCs can be hence considered non-hematopoietic multi-potent stem-like cells that are capable of differentiating into both mesenchymal and non-mesenchymal lineages. In fact, in addition to bone, cartilage, fat, and myoblasts, it has been demonstrated that MSCs are capable of differentiating into neurons and astrocytes in vitro and in vivo (Pittenger et al., 1999; Bianco and Gehron Robey, 2000; Jori et al., 2005; Beyer Nardi and da Silva Meirelles, 2006) (Fig. 1).

MSCs are of interest because they are easily isolated from a small aspirate of bone marrow and can be expanded through as many as 50 population doublings in about 10 weeks. As such, the cells are currently being tested for their potential use in cell and gene therapy for a number of human diseases. Nevertheless, there are still some open questions about origin, multipotentiality and anatomical localization of MSCs. As far as this latter point is concerned, it has been shown that MSCs can be isolated from different tissues other than bone marrow, which, however, is the primary source for obtaining these stem cells. MSCs have been isolated from adipose tissue, liver, tendons, synovial membrane, amniotic fluid, placenta, umbilical cord, and teeth (Prockop, 1997; Bianco and Gehron Robey, 2000; Beyer Nardi and da Silva Meirelles, 2006; Sethe et al., 2006).

Another hot issue is the lack of a single marker to clearly define MSCs. In fact, at present, MSCs are identified through a

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Mesenchymal Stem Cells: Will They Have a Role In the Clinic?

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Abstract In addition to hematopoietic stem cells (HSC), human post natal bone marrow contains another stem cell capable of giving rise to multiple mesenchymal cell lineages. Termed mesenchymal stem cells (MSCs) based on their capacity for multi-lineage differentiation, these cells can easily be obtained following a simple bone marrow aspiration procedure and subsequently expanded in culture through as many as 50 population doublings. This extensive capacity for expansion in vitro at clinical scale has recently facilitated the development of clinical trials designed to assess the safety, feasibility, and efficacy of transplanting MSC for a variety of pathological conditions. This review focuses on the background and rationale for performing clinical studies of MSC transplantation and will discuss the potential role that MSC may play in the correction or modification of human diseases. J. Cell. Biochem. Suppl. 38: 73–79, 2002.

Key words: mesenchymal; stem cell; transplantation; stromal; in vivo

Based on their pioneering studies initiated more than thirty years ago, Friedenstein et al. [1968] were the first to propose the concept that human post natal bone marrow contained a precursor cell for multiple mesenchymal cell lineages [Owen, 1988]. Over the ensuing decades, marrow stromal cells have been characterized, based largely upon their properties in vitro or following transplantation in various animal model systems [Bianco and Gehron Robey, 2000; Deans and Moseley, 2000]. The term colony-forming units fibroblastic (CFU-F) was coined by Friedenstein to describe cells isolated from the bone marrow stroma of a variety of post natal organisms that are adherent, nonphagocytic, fibroblastic, and clonogenic in nature [Friedenstein et al., 1974]. Under well-defined in vitro and in vivo conditions, a proportion of CFU-F can give rise to multiple mesenchymal tissues including bone, adipose, cartilage, myelosupportive stroma, smooth muscle, cardiomyocytes, and tendon. The term mesenchymal stem cells (MSCs) is based on the demonstration that there exist clonogenic populations of adherent human bone marrow derived cells which possess the capacity to differentiate into at least three well-defined mesenchymal cell lineages (osteocyte, adipocyte, and chondrocyte) when placed in the appropriate differentiative conditions [Pittenger et al., 1999]. Recently, methodologies describing the purification and expansion of human MSC have generated a new wave of enthusiasm for their study [Pittenger et al., 1999]. The capacity to expand MSC to clinical scale numbers has paved the way for the current trials evaluating the effects of transplanting MSC. Nevertheless, numerous controversies abound regarding the appropriate phenotypic and molecular description of MSC, the optimal conditions for their purification and expansion in vitro, and the proper model systems to best define the functional properties of MSC following transplantation. Very little is known currently regarding the behavior and fate of MSC following either systemic infusion or local implantation. Further, while it is envisioned, it is as of yet unproven that MSC can serve as useful tools for genetic modification in skeletal

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Review

Mesenchymal stem cells: a new trend for cell therapy

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Mesenchymal stem cells (MSCs), the major stem cells for cell therapy, have been used in the clinic for approximately 10 years. From animal models to clinical trials, MSCs have afforded promise in the treatment of numerous diseases, mainly tissue injury and immune disorders. In this review, we summarize the recent opinions on methods, timing and cell sources for MSC administration in clinical applications, and provide an overview of mechanisms that are significant in MSC-mediated therapies. Although MSCs for cell therapy have been shown to be safe and effective, there are still challenges that need to be tackled before their wide application in the clinic.

Keywords: mesenchymal stem cell; cell therapy; tissue injury; degenerative disease; immune disorder; graft-versus-host disease; immunomodulation; trophic factor

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Introduction

Stem cells are unspecialized cells with the ability to renew themselves for long periods without significant changes in their general properties. They can differentiate into various specialized cell types under certain physiological or experimental conditions. Cell therapy is a sub-type of regenerative medicine. Cell therapy based on stem cells describes the process of introducing stem cells into tissue to treat a disease with or without the addition of gene therapy. Hematopoietic stem cells (HSCs) have been widely used for allogeneic cell therapy. The successful isolation of pluripotent embryonic stem (ES) cells from the inner cell mass of early embryos has provided a powerful tool for biological research. ES cells can give rise to almost all cell lineages and are the most promising cells for regenerative medicine. The ethical issues related to their isolation have promoted the development of induced pluripotent stem (iPS) cells, which share many properties with ES cells without ethical concerns. However, one key property of ES cells and iPS cells that may seriously compromise their utility is their potential for teratoma formation.

Due to the limitation of using ES and iPS cells in the clinic, great interest has developed in mesenchymal stem cells (MSCs), which are free of both ethical concerns and teratoma formation. These cells were first isolated and characterized by Friedenstein and his colleagues in 1974. MSCs, also called mesenchymal stromal cells, are a subset of non-hematopoietic adult stem cells that originate from the mesoderm. They possess self-renewal ability and multilineage differentiation into not only mesoderm lineages, such as chondrocytes, osteocytes and adipocytes, but also ectodermic cells and endodermic cells[1-9]. MSCs exist in almost all tissues. They can be easily isolated from the bone marrow, adipose tissue, the umbilical cord, fetal liver, muscle, and lung and can be successfully expanded *in vitro*[6-10]. The number of clinical trials on MSCs has been rising since 2004 (Figure 1). Although the "gold rush" to use MSCs in clinical settings began with high enthusiasm in many countries, with China, Europe and US leading the way (http://clinicaltrial.cn), numerous scientific issues remain to be resolved before the establishment of clinical standards and governmental regulations.

What can MSCs do?

Currently, there are 344 registered clinical trials in different clinical trial phases (Figure 2) aimed at evaluating the potential of MSC-based cell therapy worldwide. With the advancement of preclinical studies, MSCs have been shown to be effective in the treatment of many diseases, including both immune diseases and non-immune diseases (Figure 3).

MSCs in tissue repair

The wide tissue distribution and multipotent differentiation of

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