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Review

Role of mesenchymal stem cells in neurogenesis and nervous system repair

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ABSTRACT

Bone marrow-derived mesenchymal stem cells (MSCs) are attractive candidates for use in regenerative medicine since they are easily accessible and can be readily expanded *in vivo*, and possess unique immunogenic properties. Moreover, these multipotent cells display intriguing environmental adaptability and secretory capacity. The ability of MSCs to migrate and engraft in a range of tissues has received significant attention. Evidence indicating that MSC transplantation results in functional improvement in animal models of neurological disorders has highlighted exciting potential for their use in neurological cell-based therapies. The manner in which MSCs elicit positive effects in the damaged nervous system remains unclear. Cell fusion and/or 'transdifferentiation' phenomena, by which MSCs have been proposed to adopt neural cell phenotypes, occur at very low frequency and are unlikely to fully account for observed neurological improvement. Alternatively, MSC-mediated neural recovery may result from the release of soluble molecules, with MSC-derived growth factors and extracellular matrix components influencing the activity of endogenous neural cells. This review discusses the potential of MSCs as candidates for use in therapies to treat neurological disorders and the molecular and cellular mechanisms by which they are understood to act.

1. Introduction

Mesenchymal stem cells (MSCs) are stromal cells found in a wide range of adult tissues including the bone marrow. These cells are the origin of several mesodermal cell lineages, characterised by an ability to differentiate into derivatives including bone, fat, and cartilage. MSCs were originally identified as a fibroblastic cell population within the bone marrow, which is distinct from the haematopoietic lineage (Friedenstein et al., 1976). They can be readily isolated from a range of sources including bone marrow, adipose tissue, peripheral blood, umbilical cord blood, amniotic fluid, tendon and ligaments, chorionic villi of the placenta, synovial membranes, olfactory mucosa, deciduous teeth and foetal liver, lung and spleen (Delorme et al., 2010; Igura et al., 2004; in't Anker et al., 2003; Kuznetsov et al., 2001; Miura et al., 2003; Rosada et al., 2003; Salingcarnboriboon et al., 2003; Seo et al., 2004; Tome et al., 2009; Tsai et al., 2004; Vandenabeele et al., 2003). In fact it now seems that MSCs are to be found in most post-natal organs and tissues, although individual populations may display subtle differences related to their specific source tissue (da Silva Meirelles et al., 2006). The isolation of MSCs from vascular tissues (da Silva Meirelles et al., 2006), supports the theory that MSCs originate from perivascular cells (Farrington-Rock et al., 2004; Shi and Gronthos, 2003), a viewpoint that might account for the widespread distribution of MSCs in the body.

The bone marrow remains the most commonly used source for MSC isolation, and even though MSCs represent only a tiny fraction (around 0.01%) of the total marrow population (Pittenger et al., 1999), their adherent nature facilitates rapid expansion and enrichment from heterogeneous starting cultures. Thus, the most common method of MSC isolation involves aspiration of bone marrow directly onto tissue culture plasticware, where MSCs will adhere to the culture surface, while contaminating haematopoietic cells remain in suspension. MSCs appear spherical during cell division, after which they increase in size and spread out, acquiring stromal, fibroblastic morphology. As cell division continues, MSCs form colonies, and eventually monolayer cultures as these colonies merge.

Confirmation of MSC populations involves the analysis of cell-type specific markers. At present, no single definitive MSC marker exists and it is therefore common practice to monitor a panel of molecules to build highly descriptive expression profiles. For example, flow cytometry is often used to confirm MSC phenotype by examining the expression of MSC-positive cell surface markers

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such as CD29, CD44, CD54, CD55, CD73, CD90, CD105, CD106, CD117 and CD166, and negative surface markers, usually antigens of haematopoietic cells, such as CD11b, CD14, CD31, CD33, CD34 and CD45 (Pittenger et al., 1999; Shyu et al., 2006). In addition to cell surface antigens, intracellular proteins including fibronectin, vimentin and α-smooth muscle actin (α-SMA) are also positive markers for MSCs (Pittenger et al., 1999). As previously noted, much attention is currently focused on the utilisation of cell surface marker expression as a means of producing more homogenous MSC cultures by fluorescence-activated cell sorting (FACS) (Alsalameh et al., 2004; Dennis et al., 2002).

Demonstration of function remains the most convincing proof of cellular identity, and in the case of MSCs this includes proving the ability to differentiate into cells possessing phenotypes of, for example, bone, fat, and cartilaginous tissues. Such differentiation can be induced *in vitro* by the addition of specific inductive factors to the culture medium. For example, osteogenic differentiation, MSCs can be treated with a cocktail of dexamethasone, ascorbic acid 2-phosphate and β-glycerophosphate, while adipogenesis can be achieved by cyclic treatment with dexamethasone, indomethacin, insulin and 3-isobutyl-1-methylxanthine (IBMX), followed by treatment with insulin.

MSCs are regarded as exciting candidates to provide reparative/regenerative action against a variety of disease types (Pittenger et al., 1999). They are traditionally categorised as 'multipotent', since they possess the potential to differentiate into multiple, closely related cell lineages specific to their germ layer of origin (i.e. bone, fat and cartilage). It stands to reason that MSCs have attracted attention as potential candidates for the treatment of diseases affecting mesodermal tissues. However, in recent years it has become clear that MSCs could be used for neurological treatments, based on convincing evidence that their administration results in functional recovery in various animal models of neural perturbation. What remains unclear is the nature of the major mechanism(s) responsible. Three main theories have attempted to explain MSC-mediated neurogenesis/neural repair. These are, '*trans*'-differentiation, cell fusion, and paracrine activity through the release of soluble factors. While there is evidence for all three phenomena, there is debate over the contribution that each of these models can realistically make to neural recovery.

2. Possible roles for MSCs in the treatment of neurological deficits

For several reasons, MSCs are emerging as particularly strong candidates for cellular therapies (Fig. 1). First, they can be isolated from a wide range of autologous sources (Gronthos et al., 2001; Igura et al., 2004; in't Anker et al., 2003; Kuznetsov et al., 2001; Miura et al., 2003; Rosada et al., 2003; Salingcarnboriboon et al., 2003; Seo et al., 2004; Tsai et al., 2004; Vandenabeele et al., 2003), some of which are readily accessible (particularly bone marrow and adipose tissue), using robust, well-established techniques (da Silva Meirelles et al., 2006; Gronthos et al., 2001; Pittenger et al., 1999). Second, their high proliferative potential allows for rapid MSC expansion *ex vivo*, while maintaining multipotentiality. Finally, MSCs are potentially suitable for use in allogeneic as well as autologous transplantation (Aggarwal and Pittenger, 2005), because they express intermediate levels of MHC Class I antigens and negligible levels of MHC Class II antigens, as do differentiated MSC derivatives (Le Blanc et al., 2003). This means that immune responses commonly associated with allogeneic transplantation may be avoidable, thereby minimising the need for rigorous immune suppression following treatment. It has also been reported that MSCs do not express co-stimulatory molecules (Majumdar et al., 2003). Moreover, following allogeneic transplantation, MSCs have been shown to evade immune recognition and remain readily detectable in recipients at extended time points (Aggarwal and Pittenger, 2005). Transplantation of MSCs has also been associated with reduced incidence of graft-versus-host-disease (GVHD), and there are even reports of MSC transplantation being used in the treatment of GVHD (Le Blanc et al., 2004). The major clinical implications of these findings are that MSCs could potentially be transplanted between unrelated individuals.

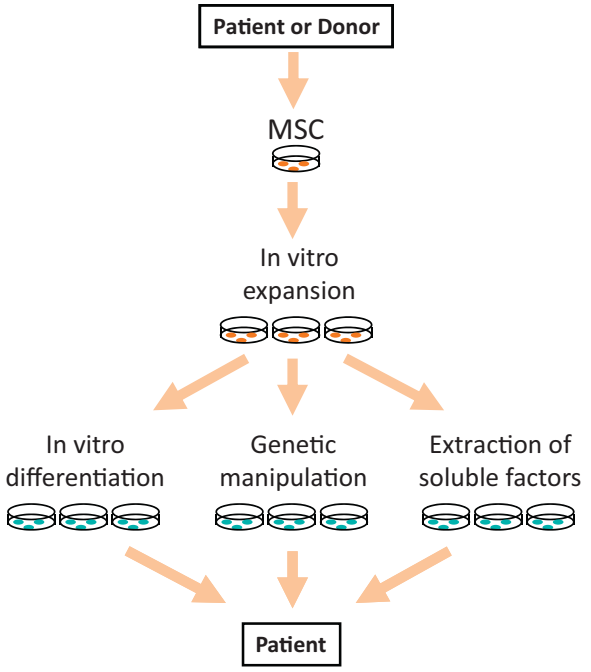

Fig. 1. Possible routes to MSC-based cell therapy. A number of key properties make MSCs strong candidates for future use in regenerative medicine. They can be readily isolated and rapidly expanded *ex vivo*, and their low immunogenicity may allow for xenographic as well as autologous transplantation. Because MSCs adapt to different microenvironments it may be possible to administer them either without prior stimulation, or following pre-differentiation or preconditioning in specific preparation for their intended use. The natural homing and secretory properties of MSCs may allow them to be exploited as vehicles for the delivery of specific therapeutic proteins following genetic manipulation. Finally, MSC-derived factors could form the basis of cell-free therapeutic cocktails.

MSCs hold clear promise as a source of cell-based therapies for a wide variety of illnesses, including those affecting the heart, bone, kidneys and skin, and a number of clinical studies have already been performed (Salem and Thiemermann, 2010). For the purposes of this review, we will focus on the potential role of MSCs as therapeutic agents in neurology.

3. Post-transplantation migration and engraftment of MSCs in the nervous system

An important first step when considering a cell type for use in regenerative medicine is to investigate the ability of that cell to migrate, engraft and survive at sites of injury.

The stem cell niche plays a crucial role in the maintenance and function of stem cells, providing a delicate balance between cell–cell interactions, extracellular matrix contact, oxygen tension, pH and exposure to growth factors, etc. (Fuchs et al., 2004). A number of studies have investigated the ability of MSCs to tolerate the essentially alien microenvironment presented by nervous tissues. Specifically, the survival and engraftment of transplanted MSCs has been assessed. It has been demonstrated that upon transplantation into the brain, MSCs can survive and undergo subsequent engraftment and migration.