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The mesenchymal stem cell secretome: A new paradigm towards cell-free therapeutic mode in regenerative medicine

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Highlights

- Cell-free therapy using MSC-CM can offer an exciting approach in regenerative medicine.
- Therapeutic role of cytokine and growth factors present in MSC-CM in clinical studies.
- Cell-free therapy offers a significant advantage over cells based therapy and other conventional pharmaceutics.

Abstract

Mesenchymal Stem Cells (MSCs) have been shown to be a promising candidate for cell-based therapy. The therapeutic potential of MSCs, towards tissue repair and wound healing is essentially based on their paracrine effects. Numerous pre-clinical and clinical studies of MSCs have yielded encouraging results. Further, these cells have been shown to be relatively safe for clinical applications. MSCs harvested from numerous anatomical locations including the bone marrow, adipose tissue, Wharton's jelly of the umbilical cord etc., display similar immunophenotypic profiles. However, there is a large body of evidence showing that MSCs secrete a variety of biologically active molecules such as growth factors, chemokines, and cytokines. Despite the similarity in their immunophenotype, the secretome of MSCs appears to vary significantly, depending on the age of the host and niches where the cells reside. Thus, by implication, proteomics-based profiling suggests that the therapeutic potential of the different MSC populations must also be different. Analysis of the secretome points to its influence on varied biological processes such as angiogenesis, neurogenesis, tissue repair, immunomodulation, wound healing, anti-fibrotic and anti-tumour for tissue maintenance and regeneration. Though MSC based therapy has been shown to be relatively safe, from a clinical standpoint, the use of cell-free infusions can altogether circumvent the administration of viable cells for therapy. Understanding the secretome of *in vitro* cultured MSC populations, by the analysis of the corresponding conditioned medium, will enable us to evaluate its utility as a new therapeutic option. This review will focus on the accumulating evidence that points to the therapeutic potential of the conditioned medium, both from pre-clinical and clinical studies. Finally, this review will emphasize the importance of profiling the conditioned medium for assessing its potential for cell-free therapy therapy.

Introduction

Stem cells have been positioned at the apex of developmental hierarchies due to their ability to self-renew and differentiate towards various cell lineages [1]. Owing to these characteristics, stem cells are now at the forefront of new therapeutic approaches for treating a number of incurable diseases that could be either lifestyle-related or primarily genetic. They play a significant role in maintaining tissue homeostasis by replacing cells in response to the requirements of physiological cell turnover in an organism. Besides this, they also play a facilitating role in replacing damaged cells with healthy cells for improving the function of injured tissues. Thus, stem cells enhance the functional capacity of an organ that has been compromised due to substantial cell loss and tissue damage. Stem cells have been majorly classified as embryonic or somatic with the former being obtained from the inner cell mass of blastocysts. Somatic stem cells, on the other hand are obtained from peri-natal or post-natal sources. Somatic stem cells include both hematopoietic stem cells (HSC) and mesenchymal stem cells (MSC) [2]. Use of somatic cells in clinical therapy is neither limited by ethical considerations nor by any safety issues relating to teratomas formation and chromosomal abnormalities [3,4]. MSCs have garnered significant interest due to their immunomodulatory capacity that could enable their use in allogeneic settings [5]. MSCs also display tissue reparative properties apart from anti-tumorigenic, anti-fibrotic, anti-apoptotic, anti-inflammatory, pro-angiogenic, neuroprotective, anti-bacterial and chemo-attractive effects [6,7]. All these traits have attracted the interest of clinician scientists and hence the vast number of clinical trials are being evidenced based on the use of MSCs.

The success of MSC transplantation relates to large scale *in vitro* expansion of therapeutically qualified cells under Good Manufacturing Practice (GMP) conditions, although a standard therapeutic cell dose of MSCs, the route of administration and the number of doses are still being optimized. Although culture expansion of MSCs has been widely used, a few issues need to be highlighted. The number of population doublings required for obtaining sufficient numbers of MSCs for therapy would be dependent on the initial number of viable MSCs. Therefore, attaining sufficient numbers could subject to a large number of population doublings with the attendant possibility of stemness attenuation and cellular senescence. Further, to avoid the risk of immunological reactions and eliminate the transmission of zoonotic disease due to the use of fetal bovine serum (FBS), MSCs are now being increasingly propagated in xeno-free media [8]. It is unclear if the data obtained from clinical trials that are based on MSCs cultured with FBS would be comparable with the data obtained with MSCs cultured in xeno-free media. There has also been a constant debate about the decline in the engraftment and homing ability, poor survival rate and impaired differentiation ability of transplanted MSCs *in vivo* limiting their therapeutic potential [9]. Due to the aforementioned issues associated with MSC-based therapy, cell free therapy using the MSC secretome could serve as a better futuristic option in the field of regenerative medicine.

Recently, evidence has accumulated supporting the effectiveness of MSC-conditioned medium (CM) or secretome in studies directed at assessing its therapeutic potential for indications such as osteoarthritis, spinal cord injury, cardiovascular disease, gastric mucosal injury, colitis etc [[10], [11], [12], [13]]. MSC-CM contains a plethora of cytokines and a wide array of bioactive factors that are secreted by MSCs. Characterization of the MSC-CM is important as its therapeutic potential has been attributed to the cytokine mixtures with their attendant paracrine activities [14]. Molecular analyses of the MSC-CM can identify key therapeutically active components that can be further purified and used. Furthermore, there would be an added interest in understanding the mechanisms by which such key components exert their therapeutic effects. Hence, the focus of this review is to summarize some of the experimental, pre-clinical and clinical studies, where the MSC secretome was tested as a treatment option with the larger goal of developing an effective cell-free based therapy.

Section snippets

Mesenchymal stem cells

MSCs are non-hematopoietic, multipotent adult stem cells that were initially isolated from the bone marrow and named colony forming unit-fibroblasts (CFU-Fs) [15]. With more than four decades of growing research on MSC populations, they have now been harvested and expanded from numerous adult and peri-natal tissues including the bone marrow (BM), adipose tissue (AT), peripheral blood, menstrual blood, pulp of deciduous teeth, umbilical cord tissue (UCT), Wharton's jelly (WJ), umbilical cord

Therapeutic characteristics of mesenchymal stem cells

The therapeutic benefits of MSCs have been well demonstrated in numerous experimental, pre-clinical and clinical models using non-clonal populations [29]. MSCs have been considered as an effective tool for tissue repair given their ability to migrate to the site of injury and their capacity to suppress the inflammatory response injury thereby promoting wound repair and healing [30]. The wound healing and tissue reparative properties have also been attributed to bioactive factors secreted by the

Cell-based therapy

Autologous and allogeneic MSCs have been used in cell-based therapies to repair and replace damaged tissues and enhance the function of tissues and organs or to exert immunomodulation *via* systemic infusions [36]. The utility of MSCs, harvested from different sources, for cell-based therapies is outlined in Fig. 1. The safety of MSC use in cell-based therapies is strongly supported by the fact that no tumours have been reported in human recipients. This has served to enhance the potential

The mesenchymal stem cell secretome

MSCs are known to secrete a spectrum of protective bio-active factors (secretome) usually classified as cytokines, chemokines, cell adhesion molecules, lipid mediators, IL, growth factors (GFs), hormones, exosomes, microvesicles, etc. These factors have been considered as protagonists to participate in tissue repair and regeneration through their paracrine actions that mediate cell-to-cell signaling [41]. The secreted molecules broadly defined as secretome or CM play a key role in influencing

Cell-free therapy

The presence of a plethora of proteins with therapeutic potential in the MSC-CM has expanded the utility of MSCs to cell-free therapy [60]. This new frontier of research provides several key advantages over cell-based applications: (a) employs the administration of proteins instead of whole cells as a new therapeutic option in regenerative medicine (b) CM can be stored without any toxic cryopreservatives such as DMSO for a relatively long period (c) preparation of CM is more economical as it

Pre-clinical studies based on the MSC secretome

A number of pre-clinical studies have demonstrated the therapeutic potential of MSC-CM for a variety of ailments such as inflammatory bowel disease (IBD), the antigen-induced model of arthritis (AIA), Parkinson's disease (PD) etc. Nevertheless, clinical trials for such indications need to be conducted to establish the therapeutic efficacy of MSC-CM.

Clinical studies based on the MSC secretome

We performed a thorough search to identify clinical studies based on the use of MSC-CM at www.pubmed.com ↗. To our knowledge, there are just two but more such studies should be initiated shortly to harness the therapeutic benefits of MSC-CM. Both these clinical studies were performed by the same group for assessing alveolar bone regeneration and angiogenesis in newly regenerated bone on administration of the secretome from hMSC. In the first report beta-tricalcium phosphate (β-TCP) or

Summary and future prospects

While results from pre-clinical studies using animal models have supported the utility of MSC-CM, much needs to be done to translate the promise to the clinic. Central to the therapeutic utility of MSC-CM would be the setting up of clinical trials for

various diseases to evaluate both the safety and efficacy of MSC-CM. With a large number of MSC-based clinical trials being approved by national agencies, obtaining regulatory approval for cell-free therapy with MSC-CM should be relatively easy.

Conflict of interests

The authors declare that they have no competing interests.

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