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Short Communication

Is it Possible to Improve the Success Rate of Cellular Therapy Based on Mesenchymal Stem Cells?

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Abstract

Non-clonal stromal cultures, containing a variable amount of Mesenchymal Stem Cells (MSCs), can be easily isolated from a small aspirate of bone marrow and expanded *in vitro*. As such, these cultures are currently used as a source of putative MSCs for therapeutic purposes.

Nowadays, dozens of clinical trials aim to treat a number of diseases, primarily immune system-related diseases, with MSCs. Moreover, several private companies are setting up clinical trials to exploit the immunomodulation and tissue repair properties of MSCs. Nevertheless, besides some successes, specifically in the treatment of immunological diseases, MSC therapies have experienced many failures. There are some issues to be analyses that may improve the success rate of MSC therapy. This editorial will briefly address some concerns associated with MSC transplants.

Keywords: Marrow stromal cells; Immunomodulation; Senescence; Stemness; Cell transplant

Introduction

Mesenchymal stem cells and their use in therapy

The micro environment of mammalian bone marrow is composed of several different elements that support hematopoiesis and bone homeostasis. It includes a heterogeneous population of cells: macrophages, fibroblasts, adipocytes, osteoprogenitors, endothelial cells, and reticular cells. Among these, there are several types of stem cells: Hematopoietic Stem Cells (HSCs), Endothelial Progenitor Cells (EPCs), and Mesenchymal Stem Cells (MSCs), which are a subset of marrow stromal cell population. MSCs differentiate into mesenchymal tissues, such as bone, cartilage and fat cells, but also support hematopoiesis and contribute to the homeostatic maintenance of many organs and tissues and, therefore, also offer significant therapeutic potential for tissue regeneration [1,2].

Non-clonal stromal cultures containing a variable amount of MSCs can be easily isolated from a small aspirate of bone marrow and expanded *in vitro*. As such, these cultures are currently used as a source of putative MSCs for therapeutic purposes. Nevertheless, there are still some open questions about the origin, multi-potentiality and anatomical localization of MSCs, as debated in several reports [2-4]. Although the nature and functions of MSCs have not been elucidated, several findings have been carried out to demonstrate the therapeutic effects of putative MSC in animal models of various diseases. In the last ten years, dozens of clinical trials were commenced to evaluate the safety and efficacy of MSC therapy. All of these investigations have clearly demonstrated that initial hypotheses about the MSC properties, which contribute to their therapeutic effects, were wrong. Initially, the therapeutic capacities of MSCs were ascribed to their homing to injured tissues and to their differentiation into various cell types [5,6]. Nevertheless, several findings showed that less than 1% of systematically administered MSCs persist for longer than a week following injection into patients [7,8].

It is now evident that therapeutic effectiveness of stromal cell transplants is based on the ability of stromal cells to secrete many bioactive molecules, which may promote the recovery of injured host cells and inhibit inflammation by their immunomodulatory activity. Some researchers also provided evidence of trophic and homeostatic functions of transplanted MSCs. There are good, reviews that analyzed in depth the limits and potentiality of the therapeutic use of MSCs [2-4].

Non-clonal cultures of MSCs secrete many growth factors, cytokines and chemokines, which have profound effects on local cellular dynamics. A thorough *in vivo* examination of this MSC secretome and strategies to modulate it are still lacking, but it seems essential for rational therapy design and for the improvement of existing therapies. Current techniques have been useful in identifying factors expressed at high levels such as IGF1, IGFBPs, interleukins, TIMP-2, VEGF, proteins involved in cell–matrix interactions and factors regulating the protein-folding response [9-12]. A limit of these studies depends on the failure to detect cytokines and growth factors that were present in low concentrations. A more systematic and integrated approach for MSC secretome analysis must include LC-MS/MS detection, antibody arrays, microarray and bioinformatics. This could be very useful in reliably identifying the MSC secretome pattern [13].

Success and failure of MSC therapy

Many clinical trials currently aim to treat a number of diseases, primarily immune system-related diseases, with MSCs or related cell-types. Moreover, several private companies are setting up clinical trials to exploit the immunomodulation and tissue repair properties of MSCs. Nevertheless, besides some successes, specifically in the treatment of immunological diseases, MSC therapies have experienced many failures. There are some issues to be analyzed that may improve the success rate of MSC therapy.

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First of all, we have to consider that MSCs currently used in therapy are non-clonal populations of bone marrow stromal cells. These mixed populations are exploited for their important role in modulating inflammation and subsequently promoting tissue repair. The use of non-clonal population in therapy is unavoidable since the clonal MSC cultures are due to insufficient numbers of daughter cells being produced. The use of non-clonal cell populations produces *per sea* higher variability in outcomes. Notwithstanding, the issue is not 'non-clonal' versus 'clonal' MSCs; rather, the issue is the standardization procedures to produce for therapeutic MSCs.

Recently, some investigators carried out meta-analysis studies to identify the potential variables affecting cellular therapies based on MSCs [14]. Donor variance, *ex vivo* expansion, immunogenicity and cryopreservation are among the main factors that can compromise the effectiveness of MSC transplants. Immunoregulatory properties of MSCs may have a significant inter-donor variability. Interferon-gamma-induced IDO (Indoleamine 2,3-Dioxygenase) upregulation may be used as a marker of immunosuppression activity. This assay has been used to demonstrate that interferon-gamma responsiveness may be quite different among individuals and that MSCs derived from low IDO inducers may be significantly less effective than cells derived from high inducers. Therefore, it could be highly useful to include an IDO responsiveness assay in screening to identify therapeutically effective MSC batches [14].

In this scenario, it should be reminded that current procedures for MSC isolation, expansion and use in therapy are standardized to isolate and cultivate a non-clonal population of stromal cells. These protocols often use the minimal criteria suggested by the International Society for Cellular Therapy (ISCT). According to ISCT, MSC must be purified from the bone marrow stromal population through plastic adherence under standard culture conditions; MSC must express at least CD73, CD90 and CD105 surface antigens and have to be CD45, CD34 negative. In addition, MSC must differentiate *in vitro* in adipocytes, chondrocytes and osteocytes [15]. These markers are quite uniform in their expression among different individual donors. Nevertheless, every non-clonal population of MSC may have a different amount of stem cells and this may affect the biological properties of the whole population. For this reason, it should be important to determine the percentage of stem/progenitor cells in each batch of MSCs that have to be delivered to patients.

Simple and reliable assays—such as Colony Forming Unit (CFU-F) assays and the evaluation of multi-potential capacity of every CFU clone—may allow the identification of the percentage of stem cells and their multi-lineage potential in every sample of non-clonal MSCs. So, if donor's MSCs were not tested for the presence and lineage potential of stem cells, it could generate a "potency bias" and eventually lead to a divergence of clinical outcomes.

Another issue that meta-analysis studies presented was *ex vivo* expansion differences. In some trials, MSC samples are heavily expanded in culture, while in other trials MSCs are grown for a limited number of *in vitro* passages. These different approaches may greatly affect the MSC properties. Indeed, *in vitro* growth of primary cells is limited by senescence, which is a cellular response to endogenous or exogenous genotoxic stress that results in an irreversible cell cycle arrest [16]. Senescent cells are non-functional cells that may also affect the activity of surrounding healthy cells. Factors secreted by senescent cells could constitute a danger signal that sensitizes normal neighboring cells to sense. In physiological conditions, this is important to reduce the chance that damaged cells at risk of neoplastic transformation would fail to enter senescence [17]. On the other hand, the presence of senescent cells in a batch of MSCs that has to be delivered to patients may greatly affect its therapeutic potential since they secreted several factors that may induce senescence of healthy neighbor cells, thus affecting the entire cell batch. It should also be emphasized, that donors' samples that will be used without *ex vivo* expansion may have a different percentage of senescent cells due to inter-individual variation. We showed that the secretive profile of MSC senescent cultures is quite different from that of young healthy cultures [12]. This may greatly affect the therapeutic performances of MSCs. In line with our research, Le Blanc showed that there is a direct positive link between early passages of MSC (with a few percentages of senescent cells) and a clinical outcome in graft-versus-host disease [14,18]. On this premise, the importance of assays aiming to evaluate the percentage of senescent cells in each batch of therapeutical MSCs is evident. Reliable methods, such as in situ-senescence associate beta galactosidase tests and related assays may allow the identification of the percentage of senescent cells in every sample of non-clonal MSCs. Also, in this case, if a donor's MSCs were not tested for the presence of senescent cells, it could generate a "potency bias" and eventually lead to a divergence of clinical outcomes.

What our research group is doing

We work with the Genkok Stem Cell Centre at Erciyes University of Kayseri (Turkey). Currently, they use mesenchymal stem cell transplants for the treatment of steroid refractory acute versus host disease. We plan to carry out a comprehensive *in vitro* analysis of stem cell batches that will be delivered to patients. On every batch, we will analyze the proliferation, senescence, cell commitment and differentiation processes. These experiments will determine to what extent the stem cell properties are divergent among the different batches of stem cells. Collected data will be used to carry out a retrospective analysis to relate to the outcome of patients, which have received a stem cell transplant, and *in vitro* stem cell properties of each batch of stem cells. We will evaluate if positive outcomes could be related to the number of stem cells in each batch of transplanted cells and to the percentage of exhausted cells (senescent cells). If positive or negative correlations will be found with the number and properties of stem cells and in the presence of senescent cells, this could pave the way to setting up new therapeutic protocols. In detail, our studies could produce recommendations stating that to have a successful transplant outcome; the batch of stem cells to be transplanted must have specific properties in terms of the number of stem cell clones and percentage of senescent cells.

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