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EDITORIAL

Mesenchymal stem cells: A new diagnostic tool?

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Abstract

Mesenchymal stem cells (MSCs) are progenitor cells capable of self-renewal that can differentiate in multiple tissues and, under specific and standardized culture conditions, expand *in vitro* with little phenotypic alterations. In recent years, preclinical and clinical studies have focused on MSC analysis and understanding the potential use of these cells as a therapy in a wide range of pathologies, and many applications have been tested. Clinical trials using MSCs have been performed (*e.g.*, for cardiac events, stroke, multiple sclerosis, blood diseases, auto-immune disorders, ischemia, and articular cartilage and bone pathologies), and for many genetic diseases, these cells are considered an important resource. Considering of the biology of MSCs, these cells may also be useful tools for understanding the physiopathology of different diseases, and they can be used to develop specific biomarkers for a broad range of diseases. In this editorial, we discuss the literature related to the use of MSCs for diagnostic applications and we suggest new technologies to improve their employment.

Key words: Mesenchymal stem cells; Biomarkers; Next generation sequencing; Diagnostic tool; Tumor-initiating cells

Core tip: Mesenchymal stem cells have been considered potential tools for therapeutic applications in a wide range of pathologies. However, these cells may be used to develop specific biomarkers in a broad range of diseases and they could be considered useful tools to perform new strategies to get early diagnoses. Rare stem cell populations can be studied by recent technologies such as Next Generation Sequencing in order to develop specific marker for diagnostic and prognostic applications.

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INTRODUCTION

Mesenchymal stem cells (MSCs) reside in many tissues during development, and their differentiation produces specific phenotypes such as osteoblasts, chondrocytes, adipocytes, and myoblasts. In recent years, MSCs have been considered an important source for cell therapy and tissue regeneration in many clinical applications. Tissue damage is followed by an inflammatory response, and pro-inflammatory factors can rescue MSCs and start the repair process. The process of regeneration is quite complex; MSCs interact with stromal and inflammatory cells, and derived factors play an important role in this process[1]. MSCs are also involved in immunosuppression *via* inhibition of T cells, B cells, dendritic cells and natural killer cells[2-5], and they may exert immunomodulatory activity during the co-transplantation process[1].

In addition to cell therapy, MSCs are also a promising choice for other clinical applications because they can be used as diagnostic tools. The involvement of MSCs in many physiological or physiopathological aspects offers the possibility of targeting these cells, and their related molecular products, circulating in peripheral blood to obtain an early diagnosis by a non-invasive approach.

Diagnostic application of MSCs

In recent years, MSCs have been considered important "biomarkers" for a non-invasive prenatal diagnosis[6]. Accurate prenatal diagnoses without fetal damage are needed to prevent genetic diseases, and MSCs have been identified in fetal blood during the first trimester, albeit at low concentrations. Despite 20 years of research in this area, technical challenges have produced many obstacles to reproducible fetal MSC isolation, and culture strategies have been developed. However, fetal MSCs have been observed in maternal peripheral blood, suggesting that fetal surface antigens could be considered promising biomarkers for a noninvasive prenatal diagnosis[7], and the analysis of neural and MSCs in the amniotic fluid represents a useful tool for the identification of neural tube defects[8].

Recruitment of progenitor cells in the blood stream in response to skeletal damage has been reported[9], and we have shown that circulating MSCs are increased in patients affected by osteoporosis as a consequence of the impairment of osteoblast differentiation[10]. Furthermore, the molecular analyses of genes involved in the differentiation process have revealed an abnormal level of expression of the transcription factor runx2, the master gene of osteogenic differentiation. These data suggest the possibility of using MSC analysis for the evaluation of bone diseases, and the identification of circulating MSCs could be proposed as a noninvasive diagnostic tool.

Circulating stem cells have been observed after ischemic stroke in patients with myocardial infarction[11,12], and this finding suggests that stem cells in the peripheral blood may provide a potential cell marker for prognosis and risk evaluation in patients with cardiac diseases.

Kim *et al*[13] showed that CD105 MSCs were mobilized in patients with cerebrovascular stroke, and, in particular, the authors demonstrated that the percentage of apoptotic CD105 cells, based on annexin V expression, was higher in patients with cerebral infarcts than that in normal control subjects.

The epithelial mesenchymal transition that occurs during cellular neoplastic transformation makes MSCs an important target for the diagnosis and prognosis of malignant tumors[14]. Because cancer may originate from the neoplastic transformation of progenitors or related early differentiated cells, stem cell-like markers expressed in tumor cells could be of interest for biomarker identification.

New technologies for stem cells

Recent technologies have made possible the study of the molecular biology of cells at different levels (*i.e*., the genome, epigenome, transcriptome, small RNAome and metabolome). However, the study of stem cells is still a major challenge due to their low numbers and their potency and plasticity. Currently, most stem cell studies reported in the literature apply microarray technology and focus on the gene expression profile analysis of MSCs[7,15-19], cancer stem cells[20-24], tumor-initiating cells[25] and embryonic stem cells. The study of gene expression at the global level is generally a pitfall and an ordeal due to the presence of low expression levels of many genes, which occurs because stem cells need to be ready to undertake a variety of differentiation programs. Accordingly, the study of different individual gene expression profiles is very difficult. Such issues cause the true gene expression signal to be confounded by background noise. At present, more recent Next Generation Sequencing (NGS) technologies[26] are entering the stem cell arena. NGS is based on massive sequencing, and it can be applied for several purposes, such as the detection of transcripts and estimation of their levels (transcriptome), the identification of genome sequence variants (exome, genome) or the examination of modified methylated nucleotides (methylome). It is noteworthy that epigenomic NGS applications[27] can be used to study stem cells because they can be used to investigate gene regulation and genome function during the differentiation and reprogramming processes. Therefore, the Epigenomics Roadmap consortium has been formed by the NIH to create extensive maps of genomic and epigenomic elements in stem cells and *ex vivo* tissue[28]. NGS methods can be used to sequence single cells (DNA and/or RNA) opening avenues to thoroughly investigate how differential gene expression in individual cells defines cellular differentiation, function and physiology[22],

making it possible to study rare stem cell populations and to investigate the prevalence and differences of potential stem cell subpopulations in cancers or other types of tissue[29].

CONCLUSION

Although several molecules such as Stro-1, CD271, SSEA-4 and CD146 are already recognized as markers for MCS cells[30], it would be useful to have even more specific markers for stem cell potential before MSC cells can serve as reliable tools for standardized diagnostic methods. In conclusion, the analysis of MSCs and their related molecular products supported by new sequencing technologies may lead to the identification of potential biomarkers that could represent useful tools for noninvasive or less invasive diagnostic and prognostic applications for a wide range of diseases. In addition, the individualization of specific markers linked to MSCs could be used to develop new strategies to obtain early diagnoses and start therapeutic approaches for patients as soon as possible.

Certainly, further investigations are necessary to validate and improve the sensitivity of specific biomarkers linked to MSCs, and innovative and costly technologies are required considering the low number and plasticity of MSCs.

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