



Editorial

Regenerative Medicine Applied to Treatment of Musculoskeletal Diseases[☆]



Medicina regenerativa aplicada al tratamiento de las patologías musculoesqueléticas

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Musculoskeletal diseases encompass a wide spectrum of diseases affecting different connective tissues of the skeletal system, including bones, cartilage, muscles, tendons and ligaments. Often, the symptoms associated with local or systemic inflammatory processes occur both acutely and chronically. Overall, they are very prevalent, and their increasing incidence and socioeconomic impact are unquestionable.^{1,2}

Skeletal muscle tissue structures are highly adapted to their function, a feature that limits their ability to structurally and functionally be restored after suffering an injury. Arthritis and joint lesions are the paradigm of musculoskeletal injury located on a complex structure, the joint, on which several skeletal tissues converge. However, the nature of musculoskeletal disease is complex and poorly understood. Due to the lack of knowledge regarding the origin of many of these diseases the current pharmacological treatment options are limited, in most cases, to controlling their symptoms rather than curing and/or preventing disease. In this context, the development of new therapies that improve existing treatments is a priority. In recent years, the most promising hopes have focused on the development and application of different techniques of regenerative medicine in order to reverse, at different levels, the damage caused by the disease.

Conceptually, although the term “regenerative medicine” includes the creation of artificial organs and their subsequent implantation, its most realistic definition refers to the set of processes used to repair or replace tissue or organ function by stimulating and inducing their own self-regeneration. Schematically, this discipline encompasses two therapeutic strategies: those based on the use of living cells or cell-based therapies and those based on tissue engineering using different scaffolds and matrices with biocompatible materials, alone or in combination, to provide support and facilitate the repair of tissue damage.³ Among cell therapies, one may differentiate 2 types of products based on mature cells, grafts or implants, and those using stem or progenitor cells.

The application of different regenerative techniques has enabled the development of different basic, preclinical and clinical studies with encouraging results for the treatment of various diseases, including those of musculoskeletal origin.^{4,5}

The first strategies to repair damage to the bone or cartilage tissue consisted of transplantation or implantation of autografts to provide a supply of cells to support an influx of osteo or chondroinducting factors. However, these methods have limitations in their bioavailability and the size of the lesion to be repaired. Alternatives such as allogeneic and/or xenogeneic transplants need further analysis regarding the risk of rejection, disease transmission and/or teratogenicity.

The therapeutic potential of each strategy depends on the nature of damage to repair. Its widespread application is still subject to the resolution of technical and biological aspects; however, advances in this field are growing, in particular those related to cellular therapies applied to musculoskeletal diseases, one of the most promising fields for medium-term treatments.^{6–8}

To understand the fundamentals and the potential of cell therapies in musculoskeletal diseases we can draw analogies with the composition of a classic drug. Not surprisingly, and bridging gaps, cellular therapies are considered drugs, and as such must meet all stages of drug development, including their adequate manufacturing practices and conditions (GMP). By definition, the principal component or ‘active ingredient’ of cell therapy is the cell itself, while the “carrier” would be represented by growth factors and/or biomaterials that facilitate structural integration or differentiation of cells. The cell component may be composed of mature or undifferentiated cells. Thus, chondrocytes or cartilage explants developed for the treatment of chondral defects are an example of the first type. However, the use of differentiated cells has not satisfactorily met expectations. Currently, attention has focused on the progenitor cells with improved biological properties and superior plasticity to those already differentiated.^{9,10}

A stem or progenitor cell is defined in terms of its ability to divide asymmetrically, i.e. self renewing itself while maintaining its undifferentiated state, or divide and differentiate into other cell types. Broadly speaking, and depending on their origin, stem cells are grouped into 2 categories: embryonic stem cells (ESC) and adult stem cells (ASC). This classification carries other intrinsic

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differentiation potential. Thus, ESC, deriving from the embryonic blastocyst can differentiate into cells belonging to any of the 3 embryonic layers: ectoderm, endoderm and mesoderm (from which skeletal tissues originate). This totipotency, however, can cause problems when undergoing therapeutic application, arising from their high proliferation capacity and the possibility of ectopic teratoma formation. Thus, the most reasonable approach, from the point of view of their therapeutic application, is to use cells with limited differentiation potential, specific to an embryonic single layer lineage.

Experimentally it is possible to induce reprogramming of adult cells to a pluripotent immature state, called *induced pluripotent stem cells* (iPSC), but its application is still under investigation. While scientific advances to avoid the risk arising from the application of the previous cell types have been made, the best current option is the use of natural skeletal progenitor cells, *mesenchymal stem cells* (MSC).

MSCs are mesodermal embryonic stem cells from which adult connective tissues develop. Therefore, they constitute progenitor cells of other specialized cells such as chondrocytes, osteoblasts, adipocytes, tenocytes, myoblasts, among others. They retain their self-renewal capacity, which facilitates their *in vitro* expansion. In addition to differentiating into different lineages, if subjected to an appropriate postimplantation stimulus *in vitro* or *in vivo*, they have immunomodulatory properties¹¹ Originally, they were described in the bone marrow stroma. They are currently known to be virtually ubiquitous, although adipose tissue along with bone marrow are the most common sources of MSC. Their frequency in tissues decreases with age,¹² and more importantly, the tissue of origin seem to confer particular characteristics that can alter their immunomodulatory properties.^{13,14} This variability may be related to the fact that MSCs are actually a heterogeneous population of cells. In fact, due to the absence of a single common tag, the definition of an MSC is performed according to the performance of three minimum criteria: their ability to adhere to culture medium, the presence of various cell surface markers and the absence hematopoietic lineage markers, and finally, their *in vitro* ability to commit to osteogenic, chondrogenic and adipogenic lineages, generally determined by histochemical staining. Given the relative laxity of the selection criteria, one of the challenges lies in the unambiguous characterization of MSC as a single entity, a task that has not yet been achieved.

The immunomodulatory functions of MSC, one of the aspects of their therapeutic potential, are gaining more importance and has already been applied in different pathologies. The study of the immunomodulatory potential of MSCs was described originally by studying their effect on regulatory T cells, such as ras initiation and mediators of transplant rejection. Numerous evidences have shown that under inflammatory conditions, MSC may inhibit T cell effector responses or increase Treg-mediated regulatory function. Furthermore, they can also exert various effects on other immune cells. Thus, MSC inhibit the maturation of dendritic cells

preventing their migration to the lymph nodes and their antigen presenting function; they modulate macrophages and NK cells, and suppress the proliferation and terminal differentiation of B¹⁵ cells. The mechanisms through which they carry out these functions are both dependent on cell contact and through secretion of soluble factors.¹⁶

Despite decades of research, safety issues have hindered, for years, regenerative medicine's potential to transform from a more generalized treatment to its application in musculoskeletal diseases. However, the bifunctional capacity of MSC to regenerate and regulate immune responses has stimulated a large number of clinical trials for different therapeutic indications which go beyond the mere provision of progenitor intended to replace lost cells or rebuild damaged tissues. At present the establishment of biobanks is a reality and the use of different products and biomaterials are part of many current clinical trials. Future efforts have to exactly determine aspects of cell biology that remain unresolved, including the pathways that determine the commitment to a particular lineage and the most appropriate therapeutic application.

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