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EDITORIAL

Stem cell therapy in vascular diseases

Terapia com células tronco em doenças vasculares

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Despite scientific advances, vascular diseases are responsible for one-third of deaths. Understanding the biology of stem cells and cell therapy could lead to a significant advance in reducing this mortality[1].

The term "stem cell" was proposed by Alexander Maksimov (1908) when developing "the unitary theory of hematopoiesis", imagining a common stem cell progenitor for all blood elements[2].

Stem cells have captured the collective imagination, with the illusion that they were a panacea for curing most diseases. While some offer stem cell therapy, most are not yet based on solid science.

The way to study stem cells in the past was through animal embryos. This held back the scientific advance, as it was ethically impossible to sacrifice a human embryo for studies[1].

In 1962 John Gurdon[3] replaced the nucleus of an embryonic frog egg with that of an adult intestinal cell. The egg turned into an embryo and later into a frog. This proved that all information to generate a new being was present in the nucleus of a mature diferentiated cell. The growth and specialization of an adult cell do not erase genes responsible for development and differentiation.

Scientists Shinya Yamanaka and Kazutoshi Takahashi in 2006 identified four genes in mice in adult cells that could produce undifferentiated cells capable of differentiating into other cells. Again, it was shown that adult cells could be reprogrammed to differentiate. In the following year, they reproduced the results in human cells[4-5].

In 2012, Yamanaka and Gurdon were awarded the Nobel Prize for Medicine and Physiology. This innovative discovery changed the view of cell development, proliferation, and differentiation[6].

The aim of cell therapy is not to simply epithelialization a wound but repair or replace tissue function and involves the restoration of blood flow, and neural and tissue regeneration[1].

Stem cells are a cell population with the capacity for self-renewal and differentiation[1]. Adult stem cells capable of differentiating into cells of mesodermal origin are called mesenchymal stromal stem cells (MSC), which also have a paracrine and immunoregulatory effect. They produce several growth factors, cytokines, and chemokines. Besides cell proliferation and

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differentiation, there are anti-apoptotic, anti-fibrotic, immunomodulatory, angiogenesis-inducing, neuroregeneration, and extracellular matrix production (collagen, proteoglycan, elastin, fibronectin, etc.) effects.

Immunomodulation occurs by inhibiting type-1 macrophage differentiation and inducing type-2 (anti-inflammatory monocytes) and by suppressing T-lymphocyte proliferation by shifting the production of pro-inflammatory Th1-lymphocytes to the anti-inflammatory Th2 subtype. There is also activation of the complement (C3) and the coagulation system (pro-coagulant effect)[1].

The most common sources for collecting these cells are bone marrow, adipose tissue, peripheral blood, and umbilical cord. However, in adults, unlike the embryo, these cells occur in small quantities and, therefore, there is a need for procedures to increase their number. Note that the older and sicker the patient, the smaller the population of stromal cells[1].

Bone marrow has been the most frequent source for collecting these cells. It is necessary to aspirate the intraosseous content of the iliac crest, but this aspirate has a heterogeneous cell population contaminated by other cells without regenerative effects. There is a need to perform washing, centrifugation, and occasionally cell culture[1].

Another source is peripheral blood due to its easy availability (puncture). However, the concentration of stromal cells is deficient and requires inducing factors such as granulocyte colony-stimulating factor (G-CSF) before cell collection and culture, which makes the method expensive[1].

The umbilical cord has been losing space to the adipose tissue, as it is autologous, readily available in adults and easily acquired through liposuction. However, liposuction has a population of heterogeneous cells without a regenerative effect.It is necessary to isolate the stromal vascular fraction (SVF), which has stem cells derived from adipose tissue, pericytes, endothelial cells, pre-adipocytes, and immune cells. The isolation of SVF is accomplished by washing, shaking, centrifugation, and even digestion by collagenase. There are semi-automated devices on the market capable of speeding up the isolation of the SVF, but due to the lack of an effective protocol, there is no good reproducibility[1].

The clinical results of cell therapy in humans with vascular diseases have been encouraging, but there is still a long way to go[7]. This therapy is safe and without significant risks and helps heal vascular ulcers, particularly in diabetic patients. However, it is still unclear what is the best type of stem cell source and the best route of administration (if systemic via intravascular or locoregional). There is also a risk of oncogenesis and thrombotic complications[7].

Currently, most human studies use bone marrow as a source (> 50%), but there is a tendency to use adipose tissue because of its ease of collection and greater availability[8]. Most use administration via direct puncture, instead of the systemic route, once such via can lead to embolism (if intra-arterially) or lose its effect by trapping in the lungs, if via the intravenous route[8]. About 90% of studies use autologous cells due to immunocompatibility, absence of transmission of infectious diseases, and ethical problems[8]. The use of cell therapy as an adjuvant to revascularization leads to better amputation-free survival and less recurrence8.

Note that there are few clinical studies and that they are heterogeneous in terms of types of disease and patients, the origin of stem cells, isolation method, administration routes, treatment protocols, and clinical outcomes[8].

In summary, stem cell therapy comprises a spectrum of regenerative strategies that depend on the following:

1) The intrinsic properties of cells, such as origin, type, and isolation methods;

2) Treatment protocol, such as dose, route of administration, and use of adjuvants; and

3) Patient specificity, such as the underlying disease, comorbidities, and immunocompetence.

Understanding and controlling the interactions between these variables and their effects are crucial to advancing cell therapy. The effectiveness and safety for its wide application are yet to be determined[1].

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