Editorial

Cell Transplantation: A New Option for Treating Cardiomyopathy

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Recent advances in molecular and cellular biology have played in integral role in the current revolution in medicine. These advances show great promise for even greater future developments. Cell transplantation therapy consists in using cells obtained from donors or from the same patient in order to recover the function of vital organs. This treatment gives rise to expectations of a cure for diseases such as coronary insufficiency and heart failure, which have thus far been considered incurable or difficult to treat. The current drug therapies and surgical techniques, such as cardiac resynchronization therapy, cardiomyoplasty, partial left ventriculectomy, plastic surgery or replacement of the mitral valve, and the use of an artificial ventricle, aim at restoring the heart's geometry without acting on the basic cause of the disease, which is cardiomyocyte death. Despite treating the basic cause, a heart transplant is restricted both by the need for organ donation and the difficulties occurring during post-operative. On the other hand, cardiomyocytes are known to be highly differentiated cells that stop their multiplication soon after the first years of life. Therefore, heart growth results from hypertrophy and not from cell hyperplasia. Cardiomyocyte death, e.g., as a result of myocardial infarction, causes fibrosis, which can lead to heart failure, depending on its extent.

Coronary and cardiac insufficiency are issues of public health, presenting high annual rates of morbidity and mortality in both developed and developing countries. Among the current trends in research, two methods of treating coronary and cardiac insufficiency are a major focus because they act on the origin of the pathological process. These methods include:

- the administration of angiogenic factors, with the objective of restoring the appropriate vascularization and, consequently, the myocardial perfusion; and
- muscle cell transplantation into the fibrotic myocardium, with the objective of restoring its function.

Promising experimental results that report improvement of the ventricular function have led to the initiation of several clinical studies currently underway in countries throughout the world. Interest in cell transplantation emerged from studies conducted by several authors, such as van Bekkum [1] (bone marrow transplant), Ostman et al. [2] (transplantation of Langerhans islets), Partridge et al. [3] (transplantation of myoblasts in patients with Duchenne's disease), and te Velde et al. [4] (transplantation of nerve cells in the treatment of Parkinson's disease). The early studies concerning cell colonization in the myocardium were encouraging, showing that both a healthy and an infarcted myocardium could be colonized by several contractile cell types, which has been confirmed by various cell markers.

Murry et al. [5] showed that fetal cardiomyocytes were able to survive in the transition zone between an infarcted and a healthy myocardium, offering good prospects for the colonization of an ischemic myocardium. Experimental transplantation of skeletal muscle cells [5], smooth cells [6], as well as fetal [7,8] and adult cardiomyocytes [9] into an infarcted myocardium was performed with the objective of determining the more beneficial cell type for colonization of the infarcted area. One of the main characteristics of these cells should be the ability to survive in an inhospitable or ischemic area. The survival of the cells transplanted

into the fibrotic area seems to be associated with a local mechanism of angiogenesis induced by the cell transplant, but such a mechanism is not yet clearly understood. Furthermore, it should be kept in mind that initially the cells do not contract (since they have not matured), and thus the need for energy is greatly reduced, so that an angiogenesis takes place concomitantly to the cell development, as has been shown in experiments [10]. More recently, different studies were conducted in order to determine whether cell transplantation could improve the function of an impaired myocardium. A positive response was obtained by Li et al. [11] who demonstrated improvement in the global function of the left ventricle two months after intramyocardial injection of fetal cardiomyocytes in rats with myocardial cryonecrosis (analysis was performed using the Langendorff method). Using this same type of cell [8], these results were confirmed through a bidimensional echocardiographic protocol, which made it possible to observe more precisely the improvement of the left ventricle's contractile function after transplantation.

The advantage of transplanting fetal cardiomyocytes is their ability to integrate with native cardiomyocytes and develop intercalated disks. This type of connection facilitates the transmission of electrical impulses between the transplanted and native cardiomyocytes, producing the synchronic contraction of the transplanted cells, which is an essential condition for improving cardiac function. However, ethical issues concerning the obtainment of fetal cells and the need for immunosuppressive therapy are factors that restrict clinical application. Based on the problems mentioned above, a search was initiated for new types of cells able to improve myocardial function. Among the several types of cells studied, those from bone marrow and autologous skeletal myoblasts seemed to be the most promising. Bone marrow contains multipotent progenitor cells (mesenchymal stem cells), which are still in the undifferentiated state and present a high proliferative capacity. In vitro studies show the capacity of such cells to differentiate into bone, tendon, fat, and muscle. Tomita et al. [15], who studied a complex cell culture with 5-azacitidine, suggested that 30% of these cells could differentiate into cardiomyocytes with fetal characteristics, with intercalated disks and myotubes. Despite the interesting and promising prospects for the recovery of myocardial viability, the culture of stem cells brought about two important questions:

- Would it be possible to cultivate a sufficiently large number of cells to colonize the infarcted region?
- As it is a stem cell differentiating into muscle cell, what would be the risk of developing another type of cell in the myocardium instead of the cardiomyocyte?

Myoblasts, the precursor cells of skeletal muscle fibers, are found in a dormant form in every skeletal muscle. They can become activated, proliferate, and differentiate into skeletal muscle fiber as a response to a physical injury in vivo, or in a cell culture medium in vitro. Studies conducted by Chiu et al. [11] and Murry et al. [5] have demonstrated the ability of these cells to proliferate, differentiate, and colonize when transplanted into infarcted hearts. Taylor et al. [12] achieved an important improvement in the cardiac function by transplanting myoblasts into cryoinjured rabbit hearts. Another study [14] compared the transplantation of skeletal myoblasts with that of adult cardiac cells into an infarcted myocardium. Results showed a restriction of left ventricular dilation and stabilization of the left ventricular ejection fraction in the group that received cardiac cells, suggesting an anti-remodeling effect. The group that received myoblastic cells showed a significant increase in the ejection fraction with preservation of the contractile activity, although with left ventricular dilation. A conclusive study for the use of skeletal myoblasts in this kind of treatment was the functional comparison with the transplantation of cardiomyocytes. One month after the transplantation in animals previously infarcted, a similar improvement of the left ventricular ejection fraction was observed in both groups. This achievement was extremely encouraging, for although myoblasts did not present intercalated disks, they were able to produce a functional improvement very similar to that obtained with fetal cardiomyocytes.

After several years of experimental studies, health authorities in France authorized myoblast transplantation in humans, focusing on the safety of the procedure in this initial stage. The first patient to benefit from this kind of treatment had 800 million myoblasts injected in the lower area of the heart after three years of infarction (irreversible akinesia detected by echo-stress test and by the absence of viability with a positron emis-

sion tomography scan). Three months later, a recovery of the contractile activity in the lower wall was observed, with an increase in the left ventricular ejection fraction from 20% to 38%. It should be emphasized that the simultaneous revascularization of the anterolateral wall of the left ventricle was also performed in this patient, probably another reason for such improvement in the ejection fraction. However, what really confirmed the effectiveness of the procedure were two new positron emission tomography scans (at 2 and 4 months) that identified muscular colonization in the previously infarcted area. There are still many questions concerning cell transplantation: Is there fatigue of the transplanted cells? What is the durability of such cells? How can transplanted cells be stimulated, since no intercalated disks were observed?

What should be emphasized most of all is the consistency of experimental studies, which have effectively demonstrated improvement of the ventricular function after transplantation. Based on the studies using these two types of cells, we have developed a technique for co-culture of such cells in our laboratory. Promising results have been obtained regarding cell expansion (compared with isolated cell cultures), the formation of new vessels, and the presence of cells transplanted into the fibrotic region in trials involving animals. At the moment, we are waiting for the approval of the results and authorization from the Ministry of Health for using these cells in a clinical study. However, only multicenter studies involving a substantial number of patients will demonstrate the effectiveness of these new therapies based on biotechnology, the most promising science of the 21st century.

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