Cellular Myogenic and Angiogenic Therapy for Myocardial Regeneration

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Follow up of congestive heart failure (CHF) patients has mobilized a growing number of research teams over the past years. Medical treatment (particularly with ACE inhibitors combined to beta-blockers and selective aldosterone blockers) as well as electrophysiological procedures (multisite pacing for atrial-biventricular resynchronization) have proven to be effective, improving the prognosis of the CHF patient. However, these treatments remain palliative and a lot of cardiovascular diseases still evolve towards the deficiency of the cardiac muscle.

Cardiac transplantation remains the only curative treatment of CHF, but has remained limited in its application secondary to shortage of donated organs, age of recipients, and other strict selection criteria. Implantable cardiac assist devices are still in evolution, and xenotransplantation is in the early phase of research with no clinical applications as of yet.

Ischemic myocardial disease, the main cause of heart failure, is a major public health and economic problem. Given the aging population, heart failure is becoming a bigger clinical issue and bigger financial burden. Thus, research in heart failure is of relevant interest and importance, involving specialities as cellular and molecular biology, genetics, biophysics and biomedical engineering.

Historically, tissue regeneration techniques based in cell transplantation technology had been used for the treatment of hemopathies (chronic lymphocytic leukemia, aplastic anaemia, immunodeficiencies, myeloma), in ophthalmology (transplantation of limbal stem cells for corneal regeneration), and in orthopedics (implantation of chondrocytes for articular defects). Current clinical investigations concern the following specialities: endocrinology (transplantation of Langerhans islets in diabetes mellitus), neurology (Huntington and Parkinson diseases, spinal cord regeneration), hepatology (implantation of hepatocytes as a bridge to liver transplantation), myology (transplantation of myoblasts in Duchenne dystrophy), in dermatology (implantation of cultured keratinocytes in burned patients) and for peripheral vascular diseases (implantation of angiogenic stem cells in chronic ischemic limbs).

Cellular Cardiomyoplasty

The prevalence of severe heart failure and the clear clinical limitations of conventional interventions have encouraged the development of new methods based on the regeneration of the pool of myocardial contractile cells. This approach is supported by recent advances in cellular and molecular biology. New technologies for cell implantation, derived from interventional cardiology procedures, are emerging. Intracoronary and endoventricular catheter-based cell delivery for therapeutic angiogenesis and myogenesis have been performed.

Cellular CMP is a combination of cellular biology with cardiac surgery or with interventional cardiology. Its aim is to regenerate the myocardium in order to prolong and improve the quality of life of patients who suffer from severe chronic cardiac deficiency and who are unresponsive to medical treatment. Cellular CMP consists of in situ cell implantation intended to induce the growth of new muscle fibers and the development of angiogenesis and vasculogenesis in the damaged myocardium. Cultured autologous cells do not raise immunological, ethical, tumorgenesis or donor availability problems.

Current possibilities in cell therapy for heart failure are the transplantation into the damaged myocardium of different cell types.

* For angiogenesis and vasculogenesis the following cells can be proposed: endothelial cells (collected from the intima of arteries or veins), bone marrow-derived stem cells, circulating blood-derived progenitor cells.
* For myogenesis: skeletal myoblasts, smooth muscle cells, fetal and neonatal cardiomyocytes can be used.
Cellular Myogenesis
The mechanism by which implanted myogenic cells improve heart function remains controversial. The 2 most investigated cells for myocardial repair are skeletal myoblasts and bone marrow stem cells.

Skeletal muscle cells are able to regenerate after injury because of the presence of satellite cells. In postnatal muscle, skeletal muscle precursors (myoblasts) can be derived from satellite cells (reserve cells located on the surface of mature myofibers). When activated by appropriate stimuli, satellite cells, proliferate and differentiate into new skeletal muscle fibers. The major advantages of this cell type is that skeletal myoblasts are highly resistant to ischemia and multiply after injury, presenting a high power for multiple mitosis. At terminal differentiation, skeletal muscle myoblasts fuse to form multinucleated myotubes. Histological studies have demonstrated that following implantation in a post-infarction lesion, myoblasts merge into myotubes within the scar decreasing fibrosis. Skeletal myoblast have been implanted in myocardial infarcts, but it is not certain whether improvement in left ventricular performance is mediated by increased systolic function caused by synchronous contraction of the graft, since skeletal myoblasts are known not to contract spontaneously and histological-electromechanical connections of transplanted myoblasts with the myocardium have not been demonstrated. Moreover, denervated skeletal myoblasts could progressively become atrophic. Electrostimulation associated with cellular cardiomyoplasty was proposed by our group to transform passive cell therapy into «dynamic cellular support».

Bone marrow stem cells can undergo milieu-dependent differentiation: when transplanted in normal myocardium can become cardiocytes, but when these cells are implanted in a myocardial scar they may differentiate into fibroblasts, becoming a «scar within a scar». Experimentally, bone marrow stromal cells can be induced to differentiate into myocytes prior to transplant using a co-culture system with cardiomyocytes or by including 5-azacytidine in the cultures. These approaches may be effective in driving myocardial remodeling, however, clinical trials can be compromised in terms of potential cell mutations by azacytidine.

Cellular Angiogenesis
The main problem following implantation of myoblasts in high fibrotic infarcted myocardium seems to be the high cellular mortality, since the oxygen and nutrients supply are limitated within the scar. Furthermore, in current clinical trials the survival of the transplanted myogenic cells were probably facilitated by the angiogenesis induced by simultaneous CABGs or angioplasty procedures performed simultaneously with cell implantation. For these reasons, angiogenic therapy before myogenesis seems to be justified.

Cell-based angiogenic therapy is an interesting and safe approach in comparison with the administration of growth factors in the form of proteins, which presents risks of systemic effects inducing problematic angiogenesis in the retina, the potentiation of growth and metastasis of occult tumors intimal and arterial hyperplasia with development of atheromatous plaque. Growth factor gene therapy presents also risks related with stability, unregulated expression and adverse response to transfection vectors.

Cells Cd133+
In humans, there are pluripotent cells expressing surface antigen AC133. These cells are rich in hemangioblast progenitors and can be isolated from bone marrow or from G-CSF mobilized peripheral blood. Thereafter these cells can differentiate along the endothelial or the hematopoietic pathway forming colonies. Many scientific observations demonstrated that the AC133+ cell population includes endothelial precursors, which is of clinical relevance (eg, in the field of ischemic disorders). The CD133+ cells fulfill many criteria of true hemangioblasts. Several studies have proven the endothelial potential of the CD133+ cells in the adult and its role in postnatal blood vessel formation, becoming an ideal starting population to generate endothelial cells.

Clinical Trials
Our 15 year clinical experience with latissimus dorsi dynamic cardiomyoplasty and aortomyoplasty, and 6 year work in experimental cellular cardiomyoplasty, provide the support for the indication and management of cardiac-bioassist techniques. We underwent 2 multicenter clinical studies:

1) Myogenic Trial:
Clinical studies into myogenesis have been initiated by our group with implantation of autologous skeletal myoblasts into myocardial scar tissue. However, a number of important questions remain. The myoblasts implanted into myocardial scar have been reported to improve systolic fiber shortening, even though no syncytial integration of these cells with native myocardial fibers could be recognized because they were surrounded by the fibrous scar tissue. The main benefits of myogenic cell transplantation into an infarcted region seems to be the recovery of elasticity to the injured region, preventing cardiac thinning, chamber dilatation, and postischemic ventricular remodeling.
2) Angiogenic Trial:
This clinical study is based on the transplantation of angiogenic cells into ischemic myocardium, using a cell isolation kit «Clinimacs» produced by Miltenyi Biotec (Germany) including a magnetic separation column for AC133+ cells, which have a recognized role in postnatal blood vessel formation. This approach avoids in-vitro cell culture procedures. These mononuclear autologous cells have endothelial potential and the possibility to differentiate in pluripotent adult stem cells, it can be previously mobilized from bone marrow by administration of stimulating growth factor G-CSF. This cellular angiogenic therapy is being performed in myocardial infarction before myogenic cell transplantation in order to improve local conditions for cell survival (preconditioning). The ultimate goal is the successive association of therapeutic angiogenesis and myogenesis.

Conclusions
There is a need of new therapeutic approaches to myocardial regeneration, whose aim is to augment the effects of the loss of cardiomyocytes, which is generally considered as irreversible, and the cause of the cardiac insufficiency. Although terminal differentiation of cardiomyocytes is disputed, it appears like a permanent turnover of contractile cells, which also happens in case of cardiac insufficiency. This might not be enough to compensate the cell death due to a pathological process. In particular, myocardial infarction leaves an akinetic fibrotic scar, which with remodeling leads to ventricular dilatation and an overall loss of the mechanical function of the heart.

The mechanisms responsible for vasculogenesis and angiogenesis are not completely understood. Several growth factors are involved in regulation of endothelial differentiation, proliferation, migration, and formation of functional vessels.

The idea of transplanting single cells has a number of attractive attributes and is dependent on an ever expanding understanding of molecular basis of angiogenesis and myogenesis. Cellular therapy primary objective is to ensure the recolonization and restoration of the muscular viability and improved functional capacities of the injured cardiac tissue.

In summary, cell transplantation already offers the promise of restoring regional ventricular function, limit remodelling and stimulate angiogenesis for patients who have had an extensive myocardial infarction and probably for patients presenting dilated cardiomyopathy. Clinical feasibility of this new surgical technique has already become apparent.

Perspectives
Cellular cardiomyoplasty appears a promising technique capable of restoring ventricular function and reversing remodeling in patients following extensive myocardial infarction. It can be considered that cellular angiogenic therapy should be performed in myocardial infarction before myogenic cell transplantation in order to improve local conditions for cell survival (preconditioning). In this way, it would be suitable to recommend a clinical trial associating successively therapeutic angiogenesis and myogenesis.

The encouraging results of experimental studies have opened the way to the clinical application of cellular cardiomyoplasty in patients with akinetic and non-viable post-infarction scar and low ejection fraction. Thus, the development of cell therapy for heart failure is progressing according to a rigorous scientific methodology, from observation to experimentation to a careful evaluation of preliminary clinical results.

References

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