Creation of a New Bioartificial Myocardium: Dream or Reality?

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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 (1, 2). Thus, research in heart failure is of relevant interest and importance, involving specialities as cellular and molecular biology, tissue engineering, genetics, biophysics and electrophysiology.

CELLULAR CARDIOMYOPLASTY

Follow up of congestive heart failure patients has mobilized a growing number of research teams over the past years. In the development of new theraphies for heart failure, one of the most innovative procedures consists in the transplantation of stem cells into the myocardium for heart muscle regeneration. This approach is called “cellular cardiomyoplasty” (3, 4). Adult myocardium cannot effectively repair after infarction due to the limited number of stem cells. Thus, most of the injury is irreversible (5). For this reason, cell transplantation strategies for heart failure have been designed to replace damaged cells with cells that can perform cardiac work, either in ischemic or non-ischemic cardiomyopathies.

Grafting of healthy cells into the diseased myocardium holds enormous potential as an approach to cardiovascular pathology. The goal of cell transplantation is to grow of new muscle fibers (myogenesis) and/or to develop angiogenesis in the damaged myocardium that potentially may contribute to improve systolic and diastolic ventricular functions, and to reverse the postischemic remodeling process of the ventricular chambers (5).

The encouraging results of experimental studies (6-11) 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 and in patients presenting idiopathic and chagasic cardiomyopathies (12-15). Cultured autologous cells do not raise immunological, ethical, tumorogenesis or donor availability problems. 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.

Current possibilities in cell therapy for myocardial regeneration are the transplantation into the damaged myocardium of different types of stem cells as: autologous myoblasts (originating from a skeletal muscle biopsy) (16), bone marrow stem cells (17), peripheral blood stem cells (18), vascular endothelial cells (19), mesothelial cells (removed from a biopsy of the omentum) (20), adipose tissue stem cells (21), and embryonic pluripotent cells (22).

Tissue engineering using biological and synthetic matrix can be associated with cell therapy, the goal is to develop a bioartificial myocardium (23-29). After several years of basic and surgical research, the MAGNUM Clinical Trial (Myocardial Assistance by Grafting a New Upgraded bioartificial Myocardium) was initiated by our group (30).

DEVELOPMENT OF BIOARTIFICIAL MYOCARDIUM

The objective of cellular cardiomyoplasty is to regenerate the myocardium by the implantation of living cells. However, in ischemic disease the extracellular matrix is often disrupted or destroyed. Therefore it could be important to associate a procedure aiming at regenerating both myocardial cells and the extracellular matrix. We are currently working to evaluate the potential of a biodegradable tridimensional matrix seeded with stem cells and grafted onto the infarcted ventricle (23).

Shortly after myocardial infarction, inflammatory cells such as neutrophils, monocytes and macrophages infiltrate the infarcted zone, and then the necrotic myocytes in the injured myocardium are replaced by collagen fibers. This process uniformly occurs in the whole infarcted area, and determines the degree of early infarct expansion. Prevention of the dilation, secondary to LV remodelling, can increase cardiac performance (5).

There are two types of collagen fibers in the normal adult heart, types I and III, produced by fibroblasts and myofibroblasts. The fiber type I represents 80% of collagen protein in the heart, and type III is near to 10%. These fibers provide structural support and give the heart properties that include stiffness and resistance to deformation, they have also shown an important role as a link between contractile elements of adjacent myocytes, carrying some information useful for cell function. In the infarcted zone the extracellular myocardial matrix is modified, collagen type I decreases from 80 to 40%. After experimental studies (23), a clinical trial was initiated by our group in ischemic patients using autologous bone marrow cell implanted into the infarct scars associated with the surgical implantation onto the epicardium of a cell-seeded collagen type I matrix.

Preliminary results showed that this procedure prevented myocardial wall thinning and limited postischemic remodelling (30).

PERSPECTIVES

Cell transplantation is becoming recognized as a viable strategy to improve myocardial viability and limit infarct growth. The major challenges for future research programs are the pre-conditioning for pre-differentiation of stem cells before transplantation, the optimization of the rate of surviving cells after myocardial implantation associating angiogenic therapy with myogenic cells, and the improvement of percutaneous cell-delivery procedures (31).

The development of a bio-artificial myocardium is a new challenge, in this approach tissue engineered procedures (26-28) are associated with cell-based myocardial regeneration. The MAGNUM Clinical Trial (Myocardial Assistance by Grafting a New Upgraded bioartificial Myocardium) have been initiated by our group (30, 32). Electrostimulation associated with cellular cardiomyoplasty was proposed by our group to transform passive cell therapy into “dynamic cellular support”. In protocols using bioengineered cell-seeded collagen matrix, electrostimulation may induce the differentiation and contraction of the grafted tissue (33, 34).

REFERENCES

1) Jessup M, Brozena S. Heart failure. N Engl J Med. 2003; 348: 2007–2018.

2) Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, Witteman JC, Stricker BH. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. Eur Heart J. 2004; 25:1614-9.

3) Chachques JC, Abdel Shafy AB, Duarte F, Cattadori B, Goussef N, Shen L, Carpentier A. From dynamic to cellular cardiomyoplasty. J Card Surg 2002; 17: 194-200.

4) Chachques JC, Acar C, Herreros J, Trainini J, Prosper F, D’Attellis N, Fabiani JN, Carpentier A. Cellular cardiomyoplasty: clinical application. Ann Thorac Surg 2004; 77 : 1121-30.

5) Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation. 1990; 81: 1161-72.

6) Wang JS, Shum-Tim D, Galipeau J, Chedrawy E, Eliopoulos N, Chiu RC. Marrow stromal cells for cellular cardiomyoplasty: feasibility and potential clinical advantages. J Thorac Cardiovasc Surg 2000; 120: 999-1005.

7) Orlic D, Kajstura J, Chimenti S, Limana F, Jakoniuk I, Quaini F, Nadal-Ginard B, Bodine DM, Leri A, Anversa P. Mobilized bone marrow cells repair the infarcted heart, improving function and survival. Proc Nat Acad Sci USA. 2001; 98: 10344-9.

8) Taylor DA, Atkins BZ, Hungspreugs P, Jones TR, Reedy MC, Hutcheson KA, Glower DD, Kraus WE. Regenerating functional myocardium: Improved performance after skeletal myoblast transplantation. Nat Med. 1998; 4: 929-933.

9) Rajnoch C, Chachques JC, Berrebi A, Bruneval P, Benoit MO, Carpentier A. Cellular therapy reverses myocardial dysfunction. J Thorac Cardiovasc Surg. 2001; 121: 871-8.

10) Chachques JC, Duarte F, Cattadori B, Shafy A, Lila N, Chatellier G, Fabiani JN, Carpentier A. Angiogenic growth factors and/or cellular therapy for myocardial regeneration: a comparative study. J Thorac Cardiovasc Surg. 2004; 128: 245–53.

11) Verfaillie CM, Schwartz R, Reyes M, Jiang Y. Unexpected potential of adult stem cells. Ann N Y Acad Sci. 2003; 996: 231-4.

12) Chachques JC, Cattadori B, Herreros J, Prosper F, Trainini JC, Blanchard D, Fabiani JN, Carpentier A. Treatment of heart failure with autologous skeletal myoblasts. Herz. 2002; 27: 570-8.

13) Haider HK, Tan AC, Aziz S, Chachques JC, Sim EK. Myoblast transplantation for cardiac repair: a clinical perspective. Mol Ther. 2004; 9: 14-23.

14) Vilas-Boas F, Feitosa GS, Soares MB, Pinho-Filho JA, Mota A, Almeida AJ, Carvalho C, de Carvalho HG, de Oliveira AD, dos Santos RR. Bone marrow cell transplantation to the myocardium of a patient with heart failure due to Chagas' disease. Arq Bras Cardiol. 2004; 82: 185-7.

15) Perin EC, Dohmann HF, Borojevic R, Silva SA, Sousa AL, Mesquita CT, Rossi MI, Carvalho AC, Dutra HS, Dohmann HJ, Silva GV, Belem L, Vivacqua R, Rangel FO, Esporcatte R, Geng YJ,

Vaughn WK, Assad JA, Mesquita ET, Willerson JT. Transendocardial, autologous bone marrow cell transplantation for severe, chronic ischemic heart failure. Circulation 2003; 107: 2294-302.

16) Chachques JC, Herreros J, Trainini J, Juffe A, Rendal E, Prosper F, Genovese J. Autologous human serum for cell culture avoids the implantation of cardioverter-defibrillators in cellular cardiomyoplasty. Int J Cardiol 2004 ; 95 (Suppl 1) : S29-S33.

17) Stamm C, Westphal B, Kleine HD, Petzsch M, Kittner C, Klinge H, Schumichen C, Nienaber CA, Freund M, Steinhoff G. Autologous bone-marrow stem-cell transplantation for myocardial regeneration. Lancet 2003; 361: 45-6.

18) Schachinger V, Assmus B, Britten MB, Honold J, Lehmann R, Teupe C, Abolmaali ND, Vogl TJ, Hofmann WK, Martin H, Dimmeler S, Zeiher AM. Transplantation of progenitor cells and regeneration enhancement in acute myocardial infarction: final one-year results of the TOPCARE-AMI Trial. J Am Coll Cardiol. 2004; 44: 1690-9.

19) Narmoneva DA, Vukmirovic R, Davis ME, Kamm RD, Lee RT. Endothelial cells promote cardiac myocyte survival and spatial reorganization. Implications for cardiac regeneration. Circulation. 2004; 110: 962-968.

20) Elmadbouh I, Chen Y, Louedec L, Silberman S, Pouzet B, Meilhac O, Michel JB. Mesothelial cell transplantation in the infarct scar induces neovascularization and improves heart function. Cardiovasc Res. 2005; 68: 307-17.

21) Planat-Benard V, Menard C, Andre M, Puceat M, Perez A, Garcia-Verdugo JM, Penicaud L, Casteilla L. Spontaneous cardiomyocyte differentiation from adipose tissue stroma cells. Circ Res. 2004; 94:223–9.

22) Kehat I, Khimovich L, Caspi O, Gepstein A, Shofti R, Arbel G, Huber I, Satin J, Itskovitz-Eldor J, Gepstein L. Electromechanical integration of cardiomyocytes derived from human embryonic stem cells. Nat Biotechnol. 2004; 22: 1282-9.

23) Cortes-Morichetti M, Frati G, Schussler O, Duong JP, Lauret E, Carpentier A, Chachques JC. Association of bioartificial myocardium and cellular cardiomyoplasty for myocardial support and regeneration. Circulation. 2005; 112 (Suppl II): II-741.

24) Kutchska I, Kofidis T, Chen IY, Arai T, Sheikh AY, Hendry SL, Pearl J, Hoyt G, Connolly A, Yang PC, Gambhir SS, Robbins RC. Collagen matrices enhance survival of embryonic cardiomyoblasts following transplantation into ischemic rat hearts. Circulation. 2005; 112 (Suppl II): II-741.

25) Rogge C, Didie M, Naito H, Hermans-Borgmeyer I, Wobus AM, Field LJ, Eschenhagen T, Zimmermann WH. Generation of engineered heart tissue from embryonic stem cell derived cardiomyocytes. Circulation. 2005; 112 (Suppl II): II-14.

26) Eschenhagen T, Zimmermann WH. Engineering myocardial tissue. Circ Res. 2005; 97: 1220-31.

27) Kofidis T, Akhyari P, Boublik J, Theodorou P, Martin U, Ruhparwar A, Fischer S, Eschenhagen T, Kubis HP, Kraft T. In vitro engineering of heart muscle: artificial myocardial tissue. J Thorac Cardiovasc Surg. 2002; 124: 63-69.

28) Leor J, Cohen S. Myocardial tissue engineering: creating a muscle patch for a wounded heart. Ann NY Acad Sci. 2004; 1015: 312-319.

29) Kadner A, Zund G, Maurus C, Breymann C, Yakarisik S, Kadner G, Turina M, Hoerstrup SP. Human umbilical cord cells for cardiovascular tissue engineering: a comparative study. Eur J Cardiothorac Surg. 2004; 25:635-641.

30) Chachques JC, Trainini JC, Lago N, Mouras J, Christen AI, Cortes Morichetti M, Frati G, Schussler O. Myocardial Assistance by Grafting a New Bioartificial Upgraded Myocardium (MAGNUM Trial): Preliminary Results. Presented at the 86th Annual Meeting, American Association for Thoracic Surgery. Philadelphia (USA), May 1-3, 2006.

31) Chachques JC, El Serafi M, Azarine A, Mousseaux E, Cortes-Morichetti M, Ba M, Fabiani JN, Carpentier A. Ex-vivo MRI evaluation of local myocardial treatments : comparison between epicardial and endocardial (Cell-Fix catheter) injection. Circulation. 2005; 112 (Suppl II): II-750.

32) Chachques JC, Herreros J, Trainini JC (eds) : book “Regeneracion Cardiaca”. Editorial Magister Eos, Buenos Aires (Argentina), 2005: 205 pages.

33) Chachques JC, Salanson-Lajos C, Lajos P, Shafy A, Alshamry A, Carpentier A. Cellular cardiomyoplasty for myocardial regeneration. Asian Cardiovasc Thorac Ann. 2005; 13: 287-96.

34) Chachques JC. Method of providing a dynamic cellular cardiac support. USA Patents A2002 0124855 and A2005 0002912. http://www.uspto.gov