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A brief review on stem cell heart repair

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"Some scientists believe it is time to step back and try to figure out the mechanism by which the cells change their identity before forging ahead with experimental treatments in humans. Others say that as long as a treatment works, understanding how it works doesn't really matter."

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Abstract

Several cardiac diseases, from myocardial infarction to heart failure, are characterized by loss of cardiomyocytes, which results in a more or less severe reduction of contractility. The damage due to the loss of viable contractile tissue is worsened by the impaired conduction and increased risk of arrhythmias. The inadequacy, and in some cases the failure, of the common therapies to allow the recovery of a normal cardiac function initially lead to the opinion that heart transplantation is the only valuable tool for the treatment of patients whose life is seriously threatened. However, since heart transplantation depends on donor availability, is not risk-free and obliges a lifelong treatment to reduce rejection response, attempts have been made to induce cardiac cell regeneration by means of cell implantation. Approximately 15 years ago the first paper proposing cardiac myoplasty was published. In the last couple of years the papers on the subject have passed the hundred thousand mark.

From the first attempts with skeletal muscle myoblasts, several sources of potentially repairing cells have been used both in animal experiments and in preliminary critical trials. I will briefly present the major results obtained in the last couple of years and the limits and controversies that have also appeared, and seem to make the implant option less immediate according to some literature.

The Vertebrate heart

The heart is among the first organs to be formed in vertebrate development, and in most mammalians cardiac myocytes are fully posmytotic within hours from birth. Myocytes tend to decrease cell divisions along gestation and in human development a sharp reduction in proliferation appears after 28 weeks. While proliferation arrests, nuclei shortly keep dividing and therefore most myocytes in many mammalians are at least binucleated. A consequence of these events is an almost complete lack of new myocytes, even upon a lesion. An injury of the heart that results in cell deaths is repaired by scar tissue of fibrotic nature, and without the capability of contractile and electrical activity. The lack of electrical activity exacerbates the risk of arrhythmias and fibrillations due to reentry loops.

While the latter situation is firmly established in mammals, other vertebrates may have a higher plasticity. Many fish hearts may repair upon an experimental lesion, as well as some amphibians. Salamanders and newts are surprisingly capable of organ regeneration compared to other vertebrates. It is well known the ability of full limb regeneration in newts, with a recover of complete functionality. The same animal can heal large cardiac wounds without scar formation. This regeneration is based on the formation of blastema (Stocum, 1968), a specialized form of regenerative tissue that partly recapitulates the embryonic development.

In contrast, even fetal mouse heart shows a limited healing capability.

Healing the heart with cell transplantation

Cardiac injuries due to infarction and other causes, therefore, lead to a loss of cells that generates decreased contractility and increases the risk of fibrillations. Pharmacological therapy and revascularization can reduce the damage, but the remaining lesions are permanent. In terminal stages only heart transplantation can save the life.

In recent years many authors have suggested that cells could be reintroduced in the heart to reduce the scar extension, facilitate contraction, and even fully replace dead cells with newly functional myocytes.
Several cell types have been proposed (Peschle & Condorelli, 2005; Fukuda, 2005); such as skeletal myoblasts (Menasche, 2005), ematopoietic and stromal bone marrow derived populations, blood chord cells (Hirata et al, 2005) and more or less differentiated stem cells coming from embryonic (Kolossov et al., 2005). or fetal tissue. In more recent experiments it has been suggested that small populations of stem cells are present in the heart, and that they could be reactivated and participate in heart healing.
While the cell types proposed are numerous, only for very few of them it has been firmly established the capability to transdifferentiate into functional myocytes (Yoon et al., 2005), with electrical and contractile activity. Among them the embryonic stem cells are probably the clearest and less confusing example (Kolossov et al., 2005). Use of ES cells has been slowed by mainly ethical or religious issues, and by some doubts about their safety and immunocompatibility.
Skeletal myoblasts have been injected in human patients, but the lack of junction formation may lead to arrhythmia and transdifferentiation is not present (Menasche, 2005).
Bone marrow derived cells (BMC) are devoid of ethical issues and can be prepared from autologous extraction, as it is routinely done for various therapies, therefore avoiding immunological problems. Within BMCs different population can be separated and often the so called mesenchymal stem cells (MSC) have been selected. While MSC have been shown in special conditions to partly differentiate into myocyes, this has been achieved with aspecific drugs such as 5-azacytidine. Very limited differentiation is instead induced by coculture with adult myocytes.
In animal models several experiments have shown a general cardiac improvement after infarction and BMC injection. The transplantation appears also to be relatively safe. A safety issue has been nevertheless evidenced by the potential of stem cells to initiate gastrointestinal tumours in animals with induced *Helicobacter* infections.
The most controversial problem is whether the cells do really integrate into the heart and differentiate into vascular or contractile tissue. While initially most experiments showed very promising results, a refinement of the detection techniques has quickly quenched the enthusiasm (Loscalzo, 2004). Immunohistological markers have been shown not to be sufficient to clarify the presence of newly formed myocytes.

Animal models

Mouse is the best animal model in terms of genomic knowledge and manipulation. Unfortunately cardiac physiology of such a small and active animal is different from human physiology. A mouse heart beats several hundred times a minute, its action potential has no plateau at all, and infarction is probably only an experimental event and is almost completely absent in the natural life of the animal. It is therefore very difficult to compare manipulations performed on mice with the actual infarction and recovery in humans. Experiments in larger animals have been performed but are still very limited.

Clinical tests

While preliminary clinical tests of MSC autologous transplantation had evidenced clear improvements, more accurate studies conducted in double-blind and with larger cohorts appear to have reduced to almost nothing the difference between treated and untreated patients.

Conclusions

While cell therapy will certainly remain an important goal to achieve, we are probably now in a moment of rethinking after the initial enthusiasm, and a refinement of approaches is needed, with reconsideration of more complex models to achieve heart healing than the simple injection of autologous bone-marrow derived stem cells.
Cell and developmental biology has received a great amount of information from the early experiments that has to be carefully analyzed.

References

Fukuda K. 2005. Progress in myocardial regeneration and cell transplantation. Circ J. Dec, 69 (12): 1431-4.
Hirata Y, Sata M, Motomura N, Takanashi M, Suematsu Y, Ono M, Takamoto S. 2005. Human umbilical cord blood cells improve cardiac function after myocardial infarction. Biochem Biophys Res Commun. Feb 11, 327 (2): 609-14.
Kolossov E, Lu Z, Drobinskaya I, Gassanov N, Duan Y, Sauer H, Manzke O, Bloch W, Bohlen H, Hescheler J, Fleischmann BK. 2005. Identification and characterization of embryonic stem cell-derived pacemaker and atrial cardiomyocytes. FASEB J. Apr, 19 (6): 577-9.
Loscalzo J. 2004. Stem cells and regeneration of the cardiovascular system: facts, fictions, and uncertainties. Blood Cells Mol Dis. Jan-Feb, 32 (1): 97-99.
Menasche P. 2005. Skeletal myoblast for cell therapy. Coron Artery Dis. Mar, 16 (2): 105-110.
Menasche P. 2005. The potential of embryonic stem cells to treat heart disease. Curr Opin Mol Ther. Aug, 7 (4): 293-9.
Peschle C & Condorelli G. 2005. Stem cells for cardiomyocyte regeneration: state of the art. Ann N Y Acad Sci. Jun, 1047: 376-85.
Stocum DL. 1968. The urodele limb regeneration blastema: a self-organizing system. I. Morphogenesis and differentiation of autografted whole and fractional blastemas. Dev Biol. Nov, 18 (5): 457-80.
Yoon J, Shim WJ, Ro YM, Lim DS. 2005. Transdifferentiation of mesenchymal stem cells into cardiomyocytes by direct cell-to-cell contact with neonatal cardiomyocyte but not adult cardiomyocytes. Oct, 84 (11): 715-21.