Conclusion: Using pangenomic microarrays, we identified and compared the gene profiles of preconditioning and postconditioning versus IR in the mouse left ventricle in vivo. Among the genes jointly downregulated by preconditioning and postconditioning, Zac1 was identified as a putative cardioprotective key regulator. Indeed downregulation at the transcriptional and protein levels of Zac1 leads to cardioprotection against IR.

256

Combination of Sonic Hedgehog and a CXCR4 Antagonist improves functional recovery via an MMP-9-dependent Pathway after Myocardial Infarction

Jérome Roncalli [Orateur] (1), Marie-Ange Renault (2), Jorn Tongers (2), Tina Thorne (2), Sol Misener (2), Douglas Losordo (2)
(1) CHU Rangueil, Pôle cardio-vasculaire et métabolique, Toulouse, France – (2) Feinberg Cardiovascular Research Institute, Chicago, Etats-Unis

Background: We have shown that the Sonic Hedgehog (Shh) embryonic signalling pathway can be reactivated in myocardial infarction (MI) in adults inducing expression of pro-angiogenic factors. We hypothesized that combining Shh gene therapy and endothelial BM-derived pro-angiogenic cell mobilization by a CXCR4 antagonist, AMD3100 (AMD), could exert synergistic effects and would be superior to either single strategy for the treatment of MI.

Methods/results: In vivo, MI was induced in WT and GFP-bone marrow (BM) transplanted mice randomly assigned in 4 treatment groups: control; AMD (single dose, 5mg/kg s.c.); Shh (intramyocardial; 100µg Shh plasmid DNA at time of MI surgery); AMD+Shh group. Left ventricular ejection fraction (LVEF) was evaluated by echo up to 4 weeks post MI. AMD+Shh group exhibited the best LV function . Furthermore, combination of AMD with subtherapeutic dose of Shh resulted in a significant improvement of cardiac function recovery compared to monotherapy, highlighting its synergistic effect ($P<0.05$). Elastic staining and immunohistological analyses demonstrated reduced infarct size and increased capillary density in the AMD+Shh group (both $P < 0.05$). Combination therapy was also associated with significant increase in number of GFP-BS lectin BM-derived cells incorporated into the ischemic area ($P<0.05$). We then explored the certain potential mechanisms of the favourable effects of combination therapy. MMP-9 mRNA expression was increased in ischemic myocardium in the AMD+Shh (10-fold versus control). The positive effect on EF of combined treatment was attenuated in MMP-9 KO mice, suggesting that MMP-9 might be a key modulator of the combination therapy.

Conclusion: Pharmacological enhancement of Shh gene therapy via BM-cell mobilization by a CXCR4 antagonist is mediated via an MMP-9-dependent pathway. The combination may offer advantages in safety and feasibility by allowing lower dose gene transfer while improving outcome post-MI

257

A novel polysaccharide-based porous scaffold for cell delivery into the infarcted heart

Catherine Le Visage (1), Olivier Gournay [Orateur] (2), Najah Ben Guirat (3), Sofiane Hamidi (1), Laetitia Chaussumier (4), Richard Isnard (3), Stéphane Hatem (3), Didier Letourneur (1), Françoise Norol (5)
(1) Inserm U698, Bio-ingénierie Cardiovasculaire, CHU X. Bichat, Paris, France – (2) groupe hospitalier Pitié Salpêtrière, Cardiologie, Paris, France – (3) Inserm UMRS 956, Faculté de médecine Pierre et Marie Curie, 75013, France – (4) Inserm U790, Institut Gustave Roussy, Villejuif, France – (5) Department of Biotherapy, AP-HP, Groupe Hospitalier Pitié Salpêtrière, Paris, France

Background: Cellular cardiomyoplasty has been proposed as an attractive strategy to repair myocardial damage. One of the crucial point is the optimal delivery strategy. In the present study, we examined the use of an implantable porous scaffold for promoting bone marrow-derived mesenchymal stem cells (MSCs) survival and functions in a rat model of acute myocardial infarction.

Methods and Results: Cardiac patch was based on biodegradable polysaccharides porous scaffold. After ligation of the left anterior coronary artery, the fate of 1x106 GFP+ MSC administered either using cellularized scaffold implantation or direct injection was examined at 1 and 2 months. The number of residual GFP+ cells in the sample studied was estimated on the basis of the fluorescence emitted by a defined number of GFP+ cells used for calibration. Cellularized scaffold allowed a more efficient delivery and the difference with direct injection was significant at 2 months, with respectively 2100±1300×103 and 215±85x103 residual GFP+ cells ($p<0.03$). Cardiac tissue levels of matrix metalloproteinase-2 and -9 mRNA were similar whatever the administration conditions but a slight increase in the local production of vascular endothelial growth factor was observed at 2 months after patch implantation in comparison to direct injection ($p<0.05$). In animals having received MSC implemented on scaffold, clusters of GFP+ cells, mainly phenotypically consistent with immature MSC cells, were detected in the peri-infarct area. The increased survival using scaffold was not translated in an improved myocardial remodelling and functions with no significant difference in the LVEDD, LVESD, and FS between the 2 groups as in comparison with animals implanted with non cellularized scaffold.

Conclusions: These findings demonstrate that the implantation of cellularized grafts is safe and effective for delivering mesenchymal stem cells into damaged myocardium, and results in a better cellular engraftment compared to direct injection.

258

Post-ischemic cardiac remodeling is accelerated in diabetic rats: similarities to clinical and tissue hypothyroidism

Christos Kalofoutis (1), Georgios Galanopoulos (1), Maria Gavra (1), Alexandros Kokkinos (1), Iordanis Mourouzis (1), Jaipaul Singh (2), Constantinos Pantos [Orateur] (1), Dennis Cokkinos (3)
(1) University of Athens, Medical School, Pharmacology, Athens, Grèce – (2) UCLAN, Department of Biological and Forensic Sciences, Preston, Royaume-Uni – (3) Onassis Cardiac Surgery Center and Biomedical Research Foundation-Academy, Athens, Grèce

We investigated whether postischemic cardiac remodeling (REM) is accelerated in diabetic rats with possible involvement of thyroid hormone (TH) signaling in this response. Changes in TH signaling occur during REM after acute myocardial infarction (MI) and contribute to cardiac dysfunction.

Diabetes was induced in Wistar rats by streptozotocin injection (35mg/Kg i.p.). After 30 days diabetic rats (DM-AMI, n=9) were subjected to MI, while control rats were either sham-operated (SHAM, n=10) or subjected to MI (AMI(1), n=10). After 2 weeks, TRα1 and TRα1 expression and TH levels were measured. Hypothyroid rats by propyl-thiouracil administration (0.05%) in water for 3 weeks were subjected to MI (HYPO-AMI, n=6) while untreated MI rats served as controls (AMI(2), n=6). LV dimensions (LVEDD and LVEDS) and ejection fraction (EF%) were used to assess contractility and REM 2 weeks after MI using echocardiography. Cardiac function was markedly decreased in DM –AMI.

	Scar (mm^2)	LVEDD (mm)	LVEDS (mm)	EF%
SHAM	-----	6.5 (0.1)	3.8 (0.2)	76 (2.6)
AMI(1)	79 (4.0)	7.7 (0.2)*	5.7 (0.2)*	52 (1.5)*
DM-AMI	83 (4.9)	8.5 (0.2)**	7.0 (0.3)**	39 (2.1)**

*p<0.05 vs SHAM, **p<0.05 vs SHAM and AMI(1)

In AMI(1), TRα1 and TRβ1 protein expression were not changed significantly as compared to SHAM while in DM-AMI, both TRα1 and TRβ1 were decreased 1.7 and 1.9 fold respectively as compared to SHAM, $p<0.05$. T3 and T4 levels were not different between groups. HYPO-AMI hearts, with scar areas comparable to AMI(2) hearts [97(4.7) vs 105 (10.3), $p>0.05$], showed a similar unfavorable functional response : EF% was found to be markedly reduced [24 (0.9) in HYPO-AMI vs 36.2 (1.0) in AMI(2), $p<0.05$], while LVEDS was 8.3 (0.2) for HYPO-AMI and 7.5(0.1) for AMI(2), $p<0.05$. LVEDD equally increased in the 2 groups. Postischemic cardiac remodeling is accelerated both in hypothyroid and diabetic hearts. Tissue hypothyroidism which occurs in DM after myocardial infarction,may at least in part, account for this response.