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Results:
and angiogenesis models in-vitro, and in-vivo after MI in rats. miRNA and proteomics analyses
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Methods:
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Introduction: Cardiac-derived progenitor cells (CPC) and bone marrow mesenchymal
stem cells (BMSC) have been evaluated in clinical trials in patients after myocardial
infarction (MI). The most beneficial cell type, however, has not been determined yet. Available
evidence suggests that both cell types may exert beneficial effects in injured hearts primarily by
releasing secreted factors, particularly exosomes (Exo; nanosized vesicles). Thus, a comparison
of cardioprotective activities of Exo from these cellular sources is important for cell heart
therapy.
Methods: Right atrial appendage and sternal BM samples were collected from patients who
underwent heart valve surgery to derive CPC and BMC, respectively. Exo were isolated from
culture media conditioned by these cells. They were tested in cardiomyocyte (CMC) apoptosis
and angiogenesis models in-vitro, and in-vivo after MI in rats. miRNA and proteomics analyses
were performed.
Results: Exo-CPC were more cardioprotective and proangiogenic than Exo-BMC both in-vitro
and in-vivo, moreover Exo-CPC improved cardiac function after MI to a greater extent than
Exo-BMC (LVEF 75.37 ± 3.15% vs 58.71 ± 6.49%, p<0.01). Both Exo types were highly enriched
in a set of cardioprotective miRNA (miR14a, miR210, miR132, miR181a) compared to Exo derived
from human dermal fibroblast, which were not cardioprotective. Pregnancy-Associated Plasma
Protein-A (PAPP-A) was identified as one of the most highly enriched proteins in Exo-CPC vs.
Exo-BMC. PAPP-A on Exo-CPC induce the release of bioactive insulin-like growth factor-1 (IGF-1)
that activate IGFR, leading to the phosphorylation of Akt and ERK in recipient CMC, resulting in re-
duced apoptosis under stress conditions. Knocking-down of PAPP-A using siRNA abrogated benefits
of Exo-CPC.
Conclusions: Exo-CPC are more cardioprotective and proangiogenic than Exo-BMC, which also
show some degree of activity. The mechanism of benefit of Exo-CPC involves PAPP-A mediated ac-
tivation of IGF-1 and Akt/ERK signalling pathways.

256 The human pericardial fluid is enriched with cardiovascular-expressed microRNAs and exosomes with therapeutic potential
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The pericardial fluid (PF) surrounds the heart and is contained in the pericardial sac. PF contains
myocardial-derived factors. MicroRNAs (miRNAs) are negative posttranscriptional regulator of their
target genes. miRNAs are released in exosome (exo) and exosomal miRNAs contribute to cell-to-cell
communication.
We hypothesized that the PF contains exo of myocardial origin and it represents a niche for the ex-
change of exo-miRNAs between heart cells. Here, we have characterized for the first time, the human
PF-exo and PF-exosomal miRNAs. PF, plasma, myocardial and vascular samples were collected as leftover from aortic valve replacement
surgery. PF was submitted to a PCR-based miRNA-array (Exonorm), revealing high expression of
cardio-vascular miRNAs. By nanoparticle tracking analyses (Nanosight), particles of the exo size range
were found present in the PF (9.8±10^12 ± 2.5±10^12). PF-exo were prepared and validated by elec-
tron microscopy and western blot using exosomal markers. Next, the PF top expressed cardio-
vascular miRNAs and miRNA-122 (non-cardiovascular negative control) were measured (RT-qPCR) in
 tissue samples (to confirm the miRNA cardiovascular expression in donor patients). PF, plasma and
in PF-exo and plasma-exo. The functional status and proangiogenic potential of PF-exo were as-
sessed in cultured endothelial cells (ECs) and in mouse schema model. The contribution of miRNAs
in PF-exo effect was investigated in vitro. Cardiovascular miRNAs, but not miRNA-122, were enriched in PF and PF-exo (comparison with plas-
ma and plasma-exo), Fluorophore-tagged PF-exo were uptaken by cultured ECs and improved EC
survival, proliferation and tube formation. The proangiogenic miRNA let-7c-5p was highly expressed
in PF-exo and could be passed to ECs, decreasing its target genes (THSB2 and TIMP2) expression in
recipient ECs. MiRNA biogenesis inhibition (by DICER silencing) in cultured ECs impaired angiogen-
esis, which could be restored by PF-exo. Finally, local PF-exo delivery improved post-ischemic angi-
genesis and blood flow recovery in mice with limb ischemia. Plasma-exo did not show angiogenic
responses either in vitro or in vivo.
In conclusion, the PF contains exosomal miRNAs that might contribute to cardiovascular homeostasis
and repair.

257 Circulating microparticles of healthy origins protect against atherosclerotic vascular disease via microRNA transfer to endothelial progenitor cells
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Background: The development of atherosclerosis and cardiovascular disease is the result of mul-
tiple intermediate processes where endothelial dysfunction and vascular inflammation play key con-
tributing roles. Cell-derived microparticles (MPS), endothelial progenitor cells (EPCs) and circulating
microRNAs (miRNAs) have attracted major interest as biomarkers and potential regulators for ath-
erosclerotic vascular disease, but their involvement in the mechanisms of inflammatory processes and
vascular repair remain controversial.
Purpose: We evaluated the possible protective role of MPS and EPC-derived MPS (MPSa) of healthy
origins in atherosclerosis development as well as the mechanisms responsible for their repair capacity.
Methods: The experiments were performed on hamsters divided into: (1) simultaneously hyperten-
sive - hyperlipidemic (HH) by combining two feeding conditions for 4 months; (2,3) HH with retro-

Heart function 4 weeks after MI
orbital sinus injection containing MPs or MPEs, from control hamster, one dose per month for 4 months of HH diet, to prevent atherosclerosis (HHMP or HHMPE); (4) controls (C), age-matched normal healthy animals.

Results: The results showed that: (1) MP/MPE transplantation suppresses the development of atherosclerosis processes via: (i) the alleviation of dyslipidemia, hypertension, circulating EPC levels, cytokine/chemokine profiles (VEGF, IL-6, IL-8); (ii) the structural and functional remodeling within the vessel wall and heart in term of: distensibility/stiffness/pulse wave velocity of thoracic aorta, carotid wall thickness, systolic and diastolic function of left ventricle, left ventricular hypertrophy, lipid accumulation/contraction/relaxation in thoracic aorta, carotid and resistance arteries; (2) MPs operate as protective and delivery system for miRNAs in circulation — this was demonstrated by validating MPs/MPEs as intercellular carriers of functional Ago2-miRNA, Stau1-miRNA and Stau2-miRNA complexes; (3) MPs and MPEs protect against atherosclerotic vascular disease via transfer of miR-10a, miR-21, miR-126, miR-146a to circulating late EPCs. It mentioned that, the favorable effects of MPEs are similar to those of MPs.

Conclusion: The data indicate that MP and MPE transplantation can counteract HH diet-induced detrimental effects by their miRNA transfer to circulating EPCs mediating their function. These promising findings using MPs and MPEs as therapeutic tools for transferring miRNAs in an atherosclerotic animal model give hope to patients with cardiovascular disease.