EXOSOMES FROM HUMAN CARDIAC-RESIDENT PROGENITOR CELLS ARE MORE CARDIOPROTECTIVE THAN EXOSOMES FROM BONE MARROW MESENCHYMAL STEM CELLS VIA A PREGNANCY-ASSOCIATED PLASMA PROTEIN-A-DEPENDENT MECHANISM


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Background
Cardiac progenitor cells (CPC) transplantation improves cardiac function after myocardial infarction (MI) and both CPC and Bone marrow derived Mesenchymal stem cells (BMC) have shown promising results in clinical trials in patients after acute MI. Available exosomes support paracrine effect as the mechanism of benefit for both cell types. Recently we have shown that exosomes (Exo), actively secreted exovesicular membrane vesicles, crucial carriers of proteins, mRNAs and miRNAs between cells, represent the key component of the paracrine activity of CPC. However, the effects of Exo-CPC and Exo-BMC have not been compared for.

Methods & Results 1
Cell isolation and characterization (CPC & BMC)
Both seminal artery and right atrial appendage explant were obtained from each of 20 patients who underwent heart surgery for valve disease to derive BMC and CPC respectively. CPC were derived from the cellular outgrowth of these specimens using tissue culture technique and grown in IMDM supplemented with 20% FBS, 100U/ml penicillin and 100µg/ml streptomycin. BMC were isolated from bone marrow of the same patients. Mononuclear cells were separated by gradient centrifugation in standard calcium-depleted RPMI medium supplemented with 5% FBS, 100U/ml penicillin and 100µg/ml streptomycin. Exo were purified from CPC conditioned medium (CM-CPC) or BMC conditioned medium (BMC-CM) of cells grown for 7 days, by ultracentrifugation. Exo concentration and their size distribution were assessed by nanoparticle tracking analysis with Nanosight. Exo were also characterized by Western Blot analysis to assess the expression of TSG101.

Methods & Results 2
Exo-CPC results superior anti-apoptotic effects cell viability, TUNEL assay & WB analysis
To test the cytoprotective effects of the two Exo populations we performed in vitro experiments. Cardiomyocytes were isolated from human hearts and grown in culture for 48h. Cardiomyocytes were subjected to serum deprivation and after 12 hours incubated with Exo-CPC, Exo-BMC or Exo-NHDF respectively. Cell death was assessed by TUNEL assay. For WB analysis 48 hours after cell death induction cells were lysed and proteins isolated. Prosurvival proteins are upregulated in Exo-CPC treated CMC compared with the Exo-BMC. The opposite is true for the pro-apoptotic proteins are upregulated in Exo-BMC.

Conclusions
We have demonstrated that Exo-CPC display superior anti-apoptotic effects both in vitro and in vivo compared with patient-matched Exo-BMC. Further studies are warranted to better understand the mechanisms underlying the antiapoptotic and proangiogenic effects exerted by Exo-CPC and to develop a clinical application for the treatment of cardiovascular disease.