**Cortical Bone Stem Cells Derived Exosomes as Potent Modulator of Cardiac Immune Response and Repair After Injury**

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***Rationale:*** Cortical bone derived stem cells (CBSCs) are known to have improved growth kinetics and myocardial repair properties that are superior to other known stem cell types used. Salutary effects of CBSCs in large are mediated by paracrine secretion. Since exosomes represent an active component of released factors we tested if CBSC derived exosomes (CBSCs-Exo) can recapitulate the beneficial reparative effects of CBSCs.
***Objective:*** Determine CBSCs derived exosomes and their contents for myocardial repair.
***Methods and Results:*** Exosomes were isolated from murine CBSCs by ultracentrifugation and had typical size (30-100nm), as validated by electron microscopy and dynamic light scattering. To determine cardiac therapeutic value, CBSCs- Exo (60µg) were injected into the border zone of the mouse heart after myocardial infarction (MI). Animals injected with CBSCs-Exo had reduced infarct size and increased myocyte survival after MI injury. Interestingly, serum levels of pro-inflammatory cytokines were significantly reduced along with decreased expression of CD68+ cells in animals receiving CBSCs-Exo versus control animals. Long term analysis of CBSC-Exo animals showed improved cardiac function and contractility compared to saline treated animals concurrent with enhanced angiogenesis 6 weeks after MI. Salutary effects of CBSC-Exo were confirmed in vitro. CBSCs-Exo increased cardiac protection in NRVMs after hypoxic challenge and enhanced tube formation in HUVECs. Simultaneously, treatment of bone marrow-derived macrophages stimulated with lipopolysaccharide (LPS) and treated with CBSCs-Exo showed increased polarization towards the M2 phenotype, demonstrating an immunomodulatory capacity of CBSCs-Exo. The underlying mechanism for beneficial effects was linked to increased packaging of cardioprotective miRs including miR125, miR20 and miR18a in CBSCs-Exo confirmed by MiRNA array analysis.
***Conclusion:*** Exosomes derived from CBSCs provide a cell free system that retains the reparative power of CBSC. CBSCs-Exo augment cardiac function after myocardial injury recapitulating earlier findings with CBSCs. The packaging of cardioprotective and immune-modulatory miRs in CBSCs-Exo appears to enhance their reparative effects after MI.

Disclosure Block:
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