nm) that transport functional miRNAs, proteins, mRNAs, and lipids, playing a key role in paracrine intercellular communication. We identified a novel ability of ECFC-exosomes to promote angiogenesis and cardiac tissue repair. Administration of ECFCs to mice following experimental end-organ ischemia resulted in ECFC-exosome-dependent increase in angiogenesis. ECFC-derived exosomes were taken up by endothelial cells leading to their increased proliferation and migration, tube formation, and formation of new vessels. Administration of ECFC-exosome to a murine model of myocardial infarction prevented cardiac remodeling and heart failure. Next generation sequencing and bioinformatics analyses identified 136 miRNAs present in ECFC-exosome cargo, and factor inhibiting HIF-1α and PTEN as their potential targets in endothelial cells.

CONCLUSION: Our findings support the view that the ECFC-exosomes represent a novel therapeutic approach to improve cardiac repair and prevent the onset of heart failure after MI.

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P008
EXTRACELLULAR VESICLES FROM HUMAN HEART EXPLANT-DERIVED CELLS ATTENUATE ACTIVATION OF THE NLRP3 INFLAMMASOME IN MACROPHAGES

R Vaka, S Parent, D Davis

Ottawa, Ontario

BACKGROUND: Intramyocardial injection of heart explant-derived cells (EDCs) improves cardiac function in preclinical models of ischemic cardiomyopathy. This therapeutic benefit is partially attributable to the anti-inflammatory cargo (micro RNAs and proteins) enriched within the extracellular vesicles (EVs) released by EDCs. Recent work has shown that activation of the NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome in both immune and non-immune cells plays a critical role in promoting cardiac inflammation and adverse remodeling. Although EDC EVs are known to modulate inflammatory mediators, their effects on the NLRP3 inflammasome are not known. Therefore, we explored the ability of EDC EVs to attenuate NLRP3 inflammasome activation in macrophages, the major pro-inflammatory cell type recruited to myocardium after an ischemic insult.

METHODS AND RESULTS: EVs were isolated from EDC conditioned media (ultracentrifugation) and characterized (Nanosight & antibody array). Monocytes (THP-1) were differentiated into macrophages (PMA; 3 days) and treated with EVs (20 hours) before priming (LPS; 4 hours) and activating (nigericin; 1 hour) the NLRP3 inflammasome. Secreted caspase-1 in the culture supernatants was measured by using a bioluminescent assay (Promega). The miRNA and protein cargo within EVs was profiled using miRNA detection (Nanostring) and liquid chromatography-mass spectrometry, respectively. miRNA and protein data were analyzed using appropriate bioinformatics tools (Tam 2.0, miRWalk, and Uniprot). EV size (160$\pm$2 nm) and markers (ICAM, ALIX, CD81, CD63, EPCAM, ANXAS, TSG101, FLOT-1) confirmed EV identity. Macrophages pretreated with EVs (4E+10 EVs/mL) showed a significant attenuation in NLRP3 inflammasome induced caspase-1 vs. LPS+nigericin-only treated cells (50% lower, n=4-6, p=0.02). EV cargo profiling revealed that EVs were enriched with 22 distinct anti-inflammatory miRNAs (Tam 2.0). Specifically, 3 miRNAs (miR-21, miR-100, miR-181a, n=3) and 5 proteins (Peroxiredoxin-1, Thioredoxin-1, Caveolin-1, Sequestosome-1, n=3) abundantly found within EVs were predicted to inhibit the NLRP3 inflammasome (miRWalk & Uniprot).

CONCLUSION: EDC EVs suppress activation of the NLRP3 inflammasome in macrophages via transfer of anti-inflammatory miRNAs and proteins.

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P009
HIGH-INTENSITY STATINS COMBINED WITH EICOSAPENTAENOIC ACID (EPA) IMPROVES ENDOTHELIAL FUNCTION DURING EXPOSURE TO OXIDIZED LDL

S Sherratt, P Libby, D Bhatt, H Dawoud, T Malinski, P Mason

Beverly, Massachusetts

BACKGROUND: During atherosclerosis, endothelial cell (EC) dysfunction results in reduced nitric oxide (NO) bioavailability and increased cytotoxic peroxynitrite (ONOO$-$). This loss of NO bioavailability results in abnormal vasodilation and inflammatory changes. Eicosapentaenoic acid (EPA) administered as icosapent ethyl (IPE) reduced cardiovascular (CV) events in high-risk patients treated with statins (REDUCE-IT). We tested the effects of high-intensity statins and EPA in ECs exposed to oxidized LDL (oxLDL).

METHODS AND RESULTS: Human umbilical vein ECs (HUVECs) were pretreated with 20 mg/dL oxLDL for 20 min, then treated with atorvastatin (active metabolite, ATM) and rosuvastatin (rosuva) at 1.0 μM $\pm$ EPA (10μM) for 1 hr. Cells were stimulated with calcium and assayed for the NO/ONOO$-$ release ratio using nanosensors. ECs exposed to oxLDL showed a 60% reduction in NO release compared with vehicle (386$\pm$29 to 156$\pm$18 nM, $p< 0.001$) concomitant with a pronounced increase in ONOO$-$ release (205$\pm$31 to 283$\pm$16 nM, $p< 0.001$), resulting in a >70% decrease in the NO/ONOO$-$ release ratio ($p < 0.001$). ECs treated with ATM had an improved NO/ONOO$-$ release