Bioinspired cell-derived nanovesicles protect the heart from ischemia reperfusion injury

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Introduction: Exosomes have been proven to alleviate myocardial ischemia reperfusion (I/R) injury in preclinical studies. However, the laborious and low-yield production process of naturally secreted exosomes has been impeding their translation into clinical trials.

Purpose: We aim to develop a simple and cost-effective protocol to produce exosome mimetics, bioinspired Cell-Derived Nanovesicles (CDNs), and examine their intrinsic bioactivity in a mouse model of I/R injury.

Methods: CDNs were produced from human U937 monocytes using cell shearing approach and characterized by dynamic light scattering (DLS), nanoparticle tracking analysis (NTA) and transmission electron microscopy (TEM). Lipid composition of cells and CDNs was analysed by lipidomics. I/R injury was induced by transient occlusion of left coronary artery. Data was analysed with Mann-Whitney U test. $P<0.05$ was considered statically significant.

Results: We obtained 538 mg (protein content) of CDNs, or $3x10^9$ CDNs, via cell shearing approach from 2×10^7 cells, approximately 15 folds of exosomes via natural secretion from the same number of cells. CDNs were 125±8 nm in diameter with negative surface charge (zeta potential −7.0±0.8) and presented as double-membranous vesicles under TEM. In vitro, CDNs showed strong antioxidant activity and could be taken up by bone marrow-derived macrophages. Following intravenous administration, as demonstrated by the IVIS Spectrum imaging system, CDNs accumulated specifically in the infarct area of the heart within 3 hours. Compared with saline treatment, CDNs reduced myocardial infarct size by 31.6% ($p<0.01$) after 24 hours of I/R injury. Intriguingly, CDNs generated from human mesenchymal stem cells showed similar therapeutic efficacy. Mechanistically, CDNs inhibited infiltration of inflammatory cells (macrophages) and promoted upregulation of the anti-inflammatory cytokine interleukin 10 (IL10) in the I/R injured hearts. In the blood stream, CDNs increased IL10 protein level and exerted antioxidant activity. Furthermore, CDNs reduced I/R injury-induced cell apoptosis in the myocardium.

Conclusion: We have established a cost-effective approach to produce exosome mimetics, bioinspired CDNs, which protect the heart from I/R injury via inhibition of inflammation, oxidative stress and cardiac cell apoptosis. CDNs have intrinsic cardioprotective capability in heart injury, comparable to exosomes.