Diagnostic/Therapeutic applications of exosomes derived from patients with atrial fibrillation

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**Introduction**: Atrial fibrillation (AF), the most common type of cardiac arrhythmia, is thought to be regulated by changes in microRNA (miRNA) expression. However, the evidence for this is inconsistent. Circulating exosomes provide a promising approach to assess novel and dynamic biomarkers in human disease, due to their high stability, easy accessibility and representation of molecules from source cells. This study was conducted to compare miRNA expression patterns in circulating exosome from different types of AF patients and to investigate the possibility of clinical application as a diagnostic biomarker and therapeutic tool.

**Methods**: Exosomes were isolated from peripheral blood of paroxysmal supraventricular tachycardia (Exo-Control, n=5), paroxysmal AF (Exo-PAF, n=5), and persistent AF (Exo-PeAF, n=5) patients by using Exoquick reagent. Approaches to exosome characterization include: (1) transmission electron microscopy (TEM) to assess structure and size; (2) nanoparticle tracking analysis (NTA) to reveal size and zeta potential. To decide to focus on miRNA content of AF patient-derived exosomes, we performed the Affymetrix GeneChip miRNA 4.0 array. For atrial fibrillation cell model, HL-1 atrial cardiomyocytes were cultured in the presence of tachypacing 0.5 and 8 Hz for 8 hr. Exosomes were treated in HL-1 cells 24 hours before pacing.

**Result**: Of the total 2578 mature miRNA probe sets, 46 exosomal miRNAs were significantly upregulated by more than 1.5-fold in the persistent AF samples (but not in the paroxysmal AF samples) relative to the SVT-controls levels. Notably, five miRNAs (miRNA-103a, miRNA-107, miRNA-320d, miRNA-486, and Let7b) were upregulated by more than 4.5-fold in persistent AF, as confirmed by quantitative reverse-transcription polymerase chain reaction analysis. These miRNAs and their target genes were involved in several important biological processes (e.g., atrial function and structural changes) and AF-associated signaling pathways. In tachypacing model of HL-1 atrial cardiomyocytes, treatment with Exo-PeAF prevented tachypacing-induced shortening of action potential duration and loss of Ca2+ transient amplitude compared to Exo-PAF. In addition, AF Exosome might be regulated Ca2+ signaling pathway.

**Conclusion**: Specific exosomal miRNAs were downregulated and upregulated in the early and late stage of AF. These findings indicate that serum exosomal miRNAs might be used as novel biomarkers to predict the progression of AF. Exosome derived from AF patients improves tachypacing-induced atrial remodeling in HL-1 cardiomyocyte. Overall, AF exosomes could have a clinical application both as diagnostic biomarkers and therapeutic tools.