Multi-omics analysis to unravel age-specific alterations in plasma exosomes

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Institutes

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Introduction

Aging is a complex process associated with progressive loss of physiological function leading to several chronic diseases, including neurodegeneration. Senescent cells drive many aging phenotypes through the senescence-associated secretory phenotype (SASP) and exosomes. Exosomes are small, lipid-bilayer enclosed, cell-derived nanoparticles (30-150 nm in diameter) that play a vital role in cell-to-cell signaling via the delivery of bioactive molecules, such as proteins, microRNAs (miRNAs), lipids and metabolites. Exosome production and release vary drastically in different physiological and pathological conditions. We hypothesize that senescence-associated exosome contents, which are largely understudied, might qualify as biomarkers for aging, including neurodegenerative diseases. The major challenge in clinical applications of exosomes lies in their isolation, followed by proteomics, lipidomics, and miRNA profiling.

Methods

Human plasma from young (20-26 years) and old (60-66 years) individuals were obtained from the 'Blood Centers of the Pacific'. Plasma exosomes were isolated and enriched by size-exclusion chromatography and ultrafiltration. Exosomes were characterized by qNANO GOLD measurements (particle size distribution analysis) and western blotting for the exosome-specific markers CD9 and TSG101. Exosome protein lysates were trypsin digested and subjected to high-resolution mass spectrometry. Data were acquired in data-independent acquisition mode (DIA), followed by protein identification and quantification using Spectronaut (Biognosys). *In-silico* pathway and network analyses were performed in R and Cytoscape. The miRNA and lipid profiles from plasma exosomes from young and old individuals were determined using next-generation sequencing and mass spectrometry, respectively, followed by data integration.

Preliminary Data

We have developed a robust and efficient Data-Independent Acquisition (DIA) mass spectrometry workflow that will unlock the potential of exosomes as aging and disease biomarkers by enabling researchers to overcome the challenges associated with cell culture- and plasma-derived 'pure' exosome isolation and proteomics analysis and due to the dynamic protein range, plasma-protein contamination or exosome rupture. The first comprehensive plasma exosome spectral library, consisting of ~2,300 unique exosome proteins, is generated by combining the data-dependent acquisitions (DDA) and direct Data-Independent Acquisitions (DIA) spectral libraries which are deposited to a public repository at the SASP ATLAS (http://www.saspatlas.com/), which has enhanced the coverage of exosome proteins and aided other researchers in performing exosome biomarker studies by incorporating the library into their workflows. The study also compares plasma exosome proteins with previously reported SASP exosomes from cultured cells and urine exosomes from aged individuals to identify the unique and common exosome proteins. Our data

Novel Aspect

Construction of first comprehensive plasma exosome spectral library, and multi-omics plasma exosome analysis for aging and aging-related disease biomarker discovery.