Nanomedicine & Biotherapeutic Discovery

Extended Abstract

Exosomes: Nanoscale Packages Contain the Health-state of the Cells that Secrete them

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Abstract

How cells communicate over large or small distances has only recently become known (Figure 1). The body uses nanometer-sized exosomes, also called Extracellular vesicles [EVs], to facilitate cell communication and send signals to distant cells throughout the body. Mounting evidence indicates that programmed/triggered secretion and targeted migration of exosomes to distant cells is a fundamental aspect of cell biology that is ubiquitous in diseased and normal cells. Exosome transport occurs through extracellular body fluids including blood, cerebrospinal fluid, saliva, milk, and urine. Characterizing this fascinating class of nanovesicles offers exciting and unique insights into how intercellular biomolecular machinery remotely orchestrates physiological and pathological events at a distance. They have been described as a cellular FedEx system. Furthermore, it is being increasingly suggested that diseases such as cancer, Alzheimer's disease, and AIDS can propagate throughout the body by hijacking exosomes and disguising themselves like wolves in sheep's clothing to sneak into healthy cells. Thus, EVs are intriguing for cell biology research, their importance in various diseases, and as models for a new class of pharmaceuticals.

From the nanotechnology perspective, exosomes are truly amazing multifunctional nanoparticles. Quantitative high-speed and highresolution single-vesicle methods for isolation and characterization of exosomes derived from various biological specimens, are essential for understanding exosomes. Applications of nanotechnology tools are important to facilitate knowledge of exosome disease biomarkers, and for new therapeutics that go beyond current bulk proteomic, genomic, or lipidomic assays. Those assays often target the biomolecular complex that constitutes the exosomes with unique signatures from the cells of origin, or explore the functional effects of exosome-mediated intercellular communication. Efforts have now focused on investigating exosomal content, which is rich in mRNA, microRNA, ncRNA and double- and single-stranded DNA signatures.

This includes disordered genes, lipids or proteins [membrane, soluble, cytoplasmic, and perhaps nuclear] and protein modifications such as phosphorylation relating to cancerous, neurodegenerative, or other disease pathways. Opportunities include signatures and characterization of therapeutic response, identifying cellular [stem] cell subpopulations and cellular states, and Epithelial-Mesenchymal transitions to identify disease detection, progression, and treatment modalities. EVpedia, a public database for exosome research shows 172,080 vesicular components identified from 263 high-throughput datasets.

Our current knowledge of single exosomes is, however, desperately lacking, despite the wealth of methods applied thus far for their characterization. Basic questions concerning morphology, size, phenotype, internal or external location of constituent components, and even concentration levels remain to be elucidated using semiquantitative and quantitative characterization methodologies. These factors are hampered by two main challenges related to their nanometer dimensions and heterogeneity. It is evident that characterizing these "super-enriched information" particles at the vesicular and sub-vesicular scale has tremendous potential for understanding, diagnosing, and identifying new approaches to combat brain and other cancers, Alzheimer's disease, and other potentially exosome-mediated infectious and non-infectious diseases. In particular, more efficient nanoparticle sizing, enumeration, and phenotyping methods that provide quantitative, sensitive, and specific "visualization" of isolated EV preparation can expand and complement the much-needed confirmation of EV purity, distinct differentiation from other smaller cells, and aggregates. This will help standardize any potential methods for downstream studies in diseaseassociated exosome genomics, proteomics, and lipidomics. To better understand the role of exosomes in

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health and disease, we first need accurate individual or simultaneous measurements of exosome size, composition, concentration, and cell of origin. Nanoscale imaging techniques have captured biological processes ranging from dynamic events such as endocytosis, cancer cells, and subcellular structures to malfunctioning protein structures associated with Alzheimer and Parkinson's disease.

While much progress has been made in vesicular imaging since the discovery of exosomes using electron microscopy [EM] in the mid-1980s, we need to continue to push the limits of microscopy and imaging for exosome research. The availability of new and advanced tools with correlative techniques have made quantitative, high-resolution information on EV size, morphology, phenotype, and biomolecular characteristics of single exosomes possible. Imaging modalities such as cryogenictransmission electron microscopy [cryo-TEM], scanning electron microscopy [SEM], Field-Emission SEM [FESEM] and atomic force microscopy [AFM] have been used to assess morphology and quality of exosome preparation. AFM and FESEM studies have challenged the previous model of "cup-shaped" exosomes originally proposed from stained samples studied with TEM. Recent advances in cuttingedge nanotechnologies, and physical and biochemical know-how, are facilitating improved detection, visualization, and characterization of individual vesicles. The aim of this progress is to combine advantages of high-resolution imaging technologies with molecular phenotyping of exosomes.

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