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Title: Proteomic & Transcriptomic Landscape of Extracellular vesicles (EVs): functional insights and diagnostic potential

Presentation Summary

Two broad classes of EVs, exosomes and shed microvesicles (sMVs), which differ in size distribution and protein/RNA profiles have been described. Accruing evidence reveals subtypes within each EV class. This presentation discusses strategies for isolating and characterising EVs from both cell culture medium and body fluids.

Abstract

Secretion and exchange of EVs by most cell types is emerging as a central paradigm for intercellular communication. Although much is known about EVs there is still lack of definition as to *how many* naturally-occurring EV classes/subtypes there are and how their properties and functionalities might differ. An understanding of this problem is critical if EVs are to be fully harnessed for therapeutic applications such as regenerative medicine, vaccination against infectious disease, and EV vaccines for cancer therapeutics.

EVs modulate recipient cell behaviour by transfer of intrinsic cargo constituents such as oncogenic proteins, cytokines, infectious proteins (amyloid-β proteins, prions, malarial proteins), miRNAs, mRNAs, DNA, lipids, and metabolites. There is now an increasing awareness that EVs play a critical role in the development of diverse pathologies such as cancer (e.g., pre-metastatic niche formation), neurodegenerative disorders, and infectious diseases. Collectively, these studies have engendered significant interest in harvesting EVs for therapeutic applications - leading to several clinical and pre-clinical investigations of EV-based therapies. Additionally, many EV-containing proteins (e.g., GPC1, MIF, EGFVIII,) and RNA species (e.g., miRNA signatures) are currently being investigated for their diagnostic potential for cancer stratification.

To date, two major EV classes have been described: 30-1000 nm diameter microvesicles referred to as shed microvesicles (sMVs) or membrane blebs) and 30-150 nm diameter EVs, referred to as exosomes. Accruing evidence reveals subtypes within each EV class. sMVs are generated by directly outward budding from the plasma membrane. By contrast, exosome biogenesis involves the early/late endosomal pathway and the inward budding of multivesicular body (MVB) luminal membranes to form intraluminal vesicles (ILVs); MVBs then traffic to and fuse with the plasma membrane whereupon they release their ILV contents into extracellular space (now referred to as exosomes). Given that most EV functional studies are performed using ill-defined EV preparations, it is very difficult to ascribe function to a specific EV subtype – this has potential ramifications when designing EV therapeutics such as possible EV-subtype side-effects in clinical investigations.

In this lecture I will provide a brief overview of EV classification, discuss methods used for their isolation and characterization, and outline the diagnostic potential of EV-protein biomarkers in disease. Our recent findings show that human colon cancer-derived EVs have specific protein and RNA (mRNA, splice-variant mRNA, miRNA, and lncRNA) profiles that allow their discrimination. New advances in the role of exosomes in the tumour microenvironment (especially, exosome-dependent tumour-stromal communication), pre- metastatic niche formation, epithelial-mesenchymal transition (EMT), and mapping of vesicle surface proteins (surfaceome) will be discussed

References:

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