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Extracellular Microvesicles: The Need for Internationally Recognised Nomenclature and Stringent Purification Criteria

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Extracellular microvesicles (eMVs) are a class of membrane bound organelles secreted by various cell types [1]. eMVs include (i) exosomes: 40-100 nm diameter membraneous vesicles of endocytic origin (ii) ectosomes (also referred to as shedding microvesicles, SMVs): large membranous vesicles (50-1000 nm diameter) that are shed directly from the plasma membrane (PM) and (iii) apoptotic blebs (50-5000 nm diameter): released by dying cells. Over the last five years, the field of eMVs has witnessed tremendous growth (more than 3,500 research articles published) mainly due to their purported role in intercellular signaling and possible source of disease biomarkers. Whilst these studies have advanced our understanding of eMVs, two key problems persist that require immediate attention.

The first problem relates to the terminologies used in naming eMVs. In the past, isolated eMVs were named based on the sample source from which they were derived. For example, exosomes isolated from dendritic cells were named dexosomes, while cancer cell derived exosomes were referred to as texosomes/oncosomes and prostate cancer cell derived exosomes as prostasomes. This sample material based vesicle naming customization has lead to different nomenclatures such as epididimosomes, argosomes, exosome-like vesicles, apoptotic blebs, microparticles, promininosomes, prostasomes, dexosomes, texosomes, dex, tex, exosomes, microparticles, nanoparticles, microvesicles, shedding microvesicles, ectosomes, archeosomes and oncosomes. More importantly, this confusion in terminology has lead to typical exosome preparations sometimes being referred as microvesicles and *vice versa*. While the nomenclature standardization issue is not uncommon for any fledgling field, these terminologies need to be refined and general consensus agreed upon. In order to address this issue, naming of the vesicles should consider the *three known mechanisms* by which membrane vesicles are released into the extracellular microenvironment: exocytic fusion of multivesicular bodies resulting in 'exosomes', budding of vesicles directly from the PM resulting in 'ectosomes' and cell death leading to 'apoptotic blebs'.

The second problem relates to different methods used for purification and isolation of eMVs. When isolating eMVs, it is of paramount importance to clearly distinguish exosomes from ectosomes and apoptotic blebs to avoid cross contamination, which will undoubtedly confound interpretation of biochemical data. Despite recent advances in our understanding of eMVs, much of the published information has been obtained from impure preparations. For example, when biochemical and functional data is obtained from crude eMV preparation, it is not possible to ascribe such data to exosomes/ectosomes/apoptotic blebs. Currently, three isolation and purification protocols are widely used with minor modifications. A combination of differential centrifugation is the most commonly used protocol to isolate a specific class of eMVs; however, the resulting pellet is contaminated with co-sedimenting vesicles and protein aggregates rendering it the crudest preparation of all. Flotation of vesicles in gradients (sucrose, OptiPrep™) allows for the separation of vesicles with different buoyant densities, but vesicles with similar buoyant densities may co-sediment (e.g., pathogenic vesicles such as HIV and prions). Recently, immunoaffinity capture utilizing mABs to eMV membrane protein has been employed to isolate exosomes. This method was reported to yield high quality exosome preparations [2]. Ironically, the method has some disadvantages caused by its own strength. As the method is based on a membrane antigen, only eMVs positive to the antigen are studied while the negative population is excluded. Additionally, for the immunoaffinity method to separate out different classes of eMVs (exosomes, ectosomes and apoptotic blebs), a clear knowledge of membrane topography specific for each eMV class is needed (this information is currently lacking in the field). For example, if EpCAM is present on the membrane of exosomes, ectosomes and apoptotic blebs, the purification methodology will again yield a mixed population.

Overall, improved methods are needed to isolate and separate pure classes of eMV populations for proteomic, transcriptomic and functional studies that are designed to unravel their biological role. Until better methods are developed, the onus is on the investigators to use optimal methods to obtain close to pure eMV populations and to name them with the agreed consensus.

References

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