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LETTER TO THE EDITOR

Oncosomes – large and small: what are they, where they came from?

Dear Editor,

Terminology matters. After all this is the basis of the formal code that allows investigators to communicate, compare notes and use computational tools to access molecular databases. If the same term is assigned different or inconsistent meanings, or different terms are used to describe the same entity, communications degenerate. This is why occasional debate on what specific terms mean, where they came from, and what is their best use is a healthy exercise.

Few scientific communities experienced this problem more acutely than those of us who work on what is now collectively described as extracellular vesicles (EVs). The underlying biological complexity, technical considerations, historical reasons and cultures of different parental research fields have stimulated semantic creativity to produce a mind numbing plethora of descriptors, including terms such as exosomes, ectosomes, microvesicles, microparticles, shed vesicles, prostasomes, promininosomes, tolerosomes, apoptotic bodies, nanovesicles and several others, the meaning of which is only recently being more rigorously considered (1–3).

The case in point are EVs known as "oncosomes." At the time of this writing, there were at least 26 PubMed citations and a handful of authoritative review articles, in which the term "oncosomes" has been used (including as key word) to highlight different aspects of EV release by cancer cells (4–7). In spite of its intuitive usefulness and convenient "ring," this term is often applied in ways that have little to do with its intended meaning, circumstances under which it has been coined in our respective laboratories, ontologic efficiency or any consensus in the field. Therefore, some context may be useful in putting things in perspective towards establishing meaningful definitions.

In 2008, we described the first piece of experimental evidence that the oncogenic form (variant III) of the epidermal growth factor receptor (EGFR), EGFRvIII, which is relatively specific to human glioblastoma (GBM), is released from brain tumour cells as cargo of EVs that range between 100 and 400 nm in diameter and carry phosphatidylserine on their surfaces (8). While the biogenesis of these EVs was initially unknown, this observation signified the ability of EVs to mediate the extracellular exit of structurally and functionally abnormal, mutant and potentially transforming macromolecules (oncogenes). This feature fundamentally and qualitatively distinguishes such oncogene-containing EVs from all of their counterparts that may be produced by transformed or non-transformed cellular populations, regardless of the state, function and origin of such cells. Indeed, this is the basis of the contention that EVs could serve as reservoir of cancer-specific biomarkers recoverable from biological fluids. To highlight this uniqueness of oncogene-carrying EVs, one of us (B.M.) coined the term "oncosomes," which was included in the related manuscript (8) and reiterated in subsequent writings (9,10). Again, in this case the root particle "onco-" refers to the oncogenic molecular cargo of cancer-derived EVs.

In 2009, one of the co-authors (D.D.V.) described a process whereby amoeboid migration of metastatic prostate cancer cells triggered production of gigantic EVs ($>1{,}000$ nm to $>10{,}000$ nm) found to emanate from large protrusions of the cellular plasma membrane (11). Formation of these EVs was dependent on cellular transformation, including activation of AKT1 and EGFR pathways, and was associated with abnormal assembly of molecular cargo, including proteins and nucleic acids. This process also reflected both the oncogenic transformation and a transition to a fast migratory and highly metastatic amoeboid phenotype of cancer cells (12). These EVs were also initially referred to as "oncosomes" but were clearly structurally and morphologically unique, beyond their molecular content. To capture this cancer-related abnormal structure and content of these highly unusual EVs, they were subsequently described as "large oncosomes" (LOs), a term that has since been consistently used in original contributions on this subject (12–14).

Interestingly, LO-like EVs may have gone underreported. For example, structures with similar characteristics (microparticles or cytoplasts) have recently been implicated in modulating innate immunity at metastatic cancer sites (15), and were also observed during formation of invadopodia and cancer cell extravasation (16). Again, in this case the distinguishing feature was the biogenetic process leading to formation of very large EVs by specific types of cancer cells. Indeed, as a corollary, it may also be useful to consider additional specific terms to describe large EVs produced by non-transformed cells as discussed by Kowal et al. (1). Perhaps in this case terms such as large EVs, "megavesicles" or shed cytoplasts could be far more appropriate than "oncosomes."

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Thus, terms "oncosomes" and "large oncosomes" are not synonymous or interchangeable. They have different origins, conceptual contexts, EV size reference and contents, and were introduced at different times and for very different specific reasons by different research groups. In none of these instances, the term "oncosomes" simply refers to the fact that these EVs emanate from cancer cells as such. Instead, these descriptors are meant to highlight two different unique consequences of malignant transformation, as it intersects with cellular vesiculation processes, namely the emission of oncogenic macromolecules and abnormalities in the EV biogenesis, respectively. Arguably both of these features are important and the related terms may retain their original usefulness, but only as long as they are applied in a purposeful, meaningful and consistent manner.

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