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Response Commentary: Exosomes vs microvesicles in hematological malignancies

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The commentary by Dr. Antonella and colleagues (1) submitted in response to our review of exosomes in hematological malignancies published in *Leukemia* (2) makes an important and pertinent point. The authors ask whether a distinction should be made between various subsets of tumor-derived extracellular vesicles (EVs) present in plasma of patients with hematological malignancies. They submit that tumor-derived microvesicles (MVs) sized at 150-1,000nm and formed by cell surface membrane “blebbing” have been shown to mediate the same spectrum of biological activities as those ascribed to exosomes sized at 10-150nm. Why then separate exosomes and MVs into distinct categories of vesicles?

This question deserves serious attention and, in fact, has been in the forefront of recent attempts to establish the nomenclature of EVs (3). Unfortunately, the answer is not readily available. Despite the intense scientific scrutiny ongoing worldwide to better define subsets of EVs and their roles in cellular communication or cross-talk, no immediate solutions have emerged. The recommendation from the International Society of Extracellular Vesicles is to use the generic term “EVs” for vesicles isolated from plasma or supernatants of cultured cells by the currently available methods (4). As these methods yield mixtures of vesicles, and no set of markers distinguishing exosomes from MVs are available, this appears to be a reasonable temporary solution until standards for the EV nomenclature become available.

The argument for making a distinction between exosomes and MVs is based on the premise that while functions of these vesicle subsets might overlap, their biogenesis and molecular contents are different. The exosome origin from the endosomal compartment confers upon them a molecular cargo containing proteins that are actively being processed by the parent cell (5). In contrast, MVs contain fragments of the cytosol randomly enclosed by the blebbing cell surface membrane. Exosome formation and release from cells are strictly

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regulated by the parent cell via the engagement of the Endosome Sorting Complex Required for Transport (ESCRT) (6). The process of intraluminal invagination in multivesicular bodies (MVBs), endows exosomes with the selectively enriched protein content that resembles that of the parent cell. Also, exosomes contain MVB-related proteins (ALIX, TSG101, syntenin-1) not present in MVs. The vesicle size may be an important distinction as well, as larger MVs carry and deliver to recipient cells more of parental cytosolic components than virus-sized exosomes, potentially mediating more effective functional re-programming. Finally, the fact that tumor or normal cells have evolved two different mechanisms for distributing their contents suggests the existence of biologically significant functional diversity.

Our own studies of EVs from plasma of patients with hematological malignancies are rigorously limited to vesicles that are isolated by size exclusion chromatography (SEC), are uniformly 30-150nm in diameter and carry one or more of MVB-related markers (7). The contaminating MVs are depleted from plasma by a series of preparative centrifugations and further eliminated in the earliest void volume fraction on the SEC column (7). We have focused on tumor-derived exosomes, because we have accumulated evidence that this rigorously-defined vesicle subset is responsible for molecular and functional reprogramming of recipient cells in hematological malignancies as well as solid tumor microenvironments (8). This does not exclude the possibility that MVs may mediate similar or overlapping functions, as suggested by Dr. Antonella et al. While confident that vesicles we isolate and study are exosomes and not MVs, we realize that most of the functional studies referred to in our review or in Dr. Antonella's commentary were performed with mixtures of EVs. Ultracentrifugations or commercially-available polymer precipitation isolation methods yield mixtures of variously-sized vesicles and do not discriminate exosomes from MVs. As no “gold standard” method for EV isolation exists, individual reports, each using a different method, are likely to convey information obtained with specimens variously enriched in exosomes or MVs. We agree with Dr. Antonella's comment that the development of new methodologies and new phenotypic markers is critical for separation of different EV subsets and for reliable functional comparisons of exosome vs. MV fractions. Meanwhile, the discussion about the nomenclature and functional heterogeneity of EVs has to await further advances in their isolation and characterization.

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