Exosomes: New Advances in the Translational Potential of the "Garbage Bag"

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Bidirectional cell-cell communication via paracrine mechanisms involving nano-sized extracellular vesicles have emerged as a predominant mechanism of cellular signaling. Unlike other shedding vesicles of similar size, exosomes selectively package their cargo using defined mechanisms within the cells. Recent research on exosome signaling describes a messenger-recipient cell dichotomy. The heterogeneous origin of exosome populations, although previously described, has as-yet been incompletely characterized using this dichotomy and thus does not currently provide a complete understanding of exosome populations. In this work, we outline the fundamentally bidirectional nature of exosomes and replace this dichotomy with a messenger-recipient-effector network formed by repackaging and rerelease events. This network further confounds the determination of messenger cell identity among an already heterogeneous exosome population and has major implications for future clinical application. Redefining the axiom of exosome signaling provides a route for future research to consider a multi-system-based approach and underscores a need for enhanced identification methods. This shift also has implications for the use of exosomes as therapeutic agents. Exosome biogenesis and its manipulation will be crucial for the development of curative endogenous exosomes and their synthetic, exogenously produced counterparts. Directed cargo loading, optimal shell composition, and robust production platforms are just some of the design aspects that need to be considered. As tissue-specific therapeutic agents, exosome design will also need to incorporate repackaging mechanics to prevent off-target effects and increase efficacy. A comprehensive current understanding of exosome biogenesis mechanisms amidst the heterogenous EV population will propel the field towards clinical viability.