Editorial

Exosome mediated phenotypic changes in lung cancer pathophysiology

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Exosomes are small extracellular vesicles with a size range of 40–150 nm and a lipid bilayer membrane (1-4). They contain protein and nucleic acids, and mediate local and systemic intercellular communication (1-3). Many cell types can produce exosomes, the contents of which likely reflect the phenotypic states of the cells that generate them under both physiological and pathological conditions. They may convey these exosomal cargoes to neighboring or distant cells, and subsequently modulate the phenotype of these target cells. At first exosomes were thought to function as "cellular garbage bags", but now these nano-sized extracellular vesicles are being studied for their role in progression and metastasis (5). Cancer-derived exosomes are reported to play a role in various malignant phenotype mechanisms such as proliferation, motility, invasive properties of the recipient cells, epithelial-mesenchymal transition (EMT), transferring drug resistance, immune evasion, and pre-metastatic niche formation (6-17). However, we still need to understand how exosomes and their cargoes function in recipient cells, and whether exosome packaging and release in the extracellular space is an active or passive process.

Lobb and colleagues, in a current issue of the International Journal of Cancer, have used a human preclinical model system to study some of these issues (18). While the exosome isolation, characterization, transfer, and monitoring methods for gene expression, epithelial to mesenchymal transition (EMT), and phenotyping for resistance to chemotherapy they used were all standard, the model system studied was novel. They studied an isogenic pair of immortalized (with CDK4 and human telomerase) human bronchial epithelial cells (HBECs) one of which was the "parental" strain (HBEC30KT) and one that had been manipulated with oncogenic changes (introduction of oncogenic KRAS, knockdown of p53 and LKB1/STK11, HBEC30KT$^{p53/KRAS/LKB1}$) to progress it to malignancy and induction of EMT (18). Exosomes isolated from the non-malignant parent HBEC and from the oncogenically manipulated HBEC were then transferred to the non-malignant HBEC parent and the phenotypic changes including EMT, expression of EMT transcription factors, cancer stem cell markers and drug response phenotypes compared (18). Recent studies have shown that ZEB1 transcription factor-driven EMT promotes the loss of epithelial cell polarity and adhesion, induces cytoskeleton remodeling, and drives growth, migration, invasion, and metastasis (19-25). In the Lobb study, the oncogenic manipulated HBECs (HBEC30KT$^{p53/KRAS/LKB1}$) but not parental HBEC30KT exhibit EMT, and cancer stem cell-like and drug resistance phenotypes (18). Both HBEC30KT$^{p53/KRAS/LKB1}$ exosomes and parental HBEC30KT cells treated with HBEC30KT$^{p53/KRAS/LKB1}$-derived exosomes were enriched in ZEB1 mRNA, suggesting that the horizontal transfer

of a key EMT transcription factor, ZEB1, as exosome cargo from donor cells to target cell occurred after 24-hour co-culture. They demonstrated that HBEC30KT$^{p53/KRAS/LKB1}$ exosomes conferred EMT phenotypic changes, expression of EMT transcription factors, cancer cell stem like phenotype and chemoresistance on the parental HBEC30KT cells *in vitro*. These results raise the possibility that lung epithelial cells that have suffered oncogenic changes resulting in important malignant phenotypes can communicate these changes via the transfer of mRNAs such as ZEB1 in exosomes to other epithelial cells.

The Lobb findings raise a number of important questions (4,13-17). In addition to the model system studied by Lobb, do real human cancer cells have this capacity? Does this process occur in vivo as well as *in vitro*? What oncogenic changes can induce (or are associated with) exosomal transferred phenotypic changes? Do such exosomal induced and transferred changes only occur in the setting of EMT? Which exosomal cargoes are important in transferring malignant phenotype information including mRNA, protein, miRNAs, noncoding long RNAs, DNA or other signaling molecules? Do exosomes of the cancer stem cell subpopulation play a larger role in transferring important malignant information than exosomes from other cell subtypes in the same tumor? Does the type of recipient cell determine the response to cancer derived exosomes? What happens to the recipient cells? For example, how long lived are the changes; do they facilitate further malignant progression of the recipient including assumption of a cancer stem cell phenotype; and what are the spatial dimensions of the transfer? Are they only local or can they be distant? Which tissues can function as recipients? What types of therapeutic resistance can be transferred? Do these include resistance to targeted therapy as well as chemotherapy, and can resistance to immunotherapy be transferred? In addition, what is the magnitude of the resistance transferred? Can this exosome mediated EMT ZEB1 transfer occur in other cancer lineages besides lung cancer? Tumors and their micro-environment are a composite of cancer cells (that can exhibit genetic and phenotypic heterogeneity), immune cells, mesenchymal stem cells, fibroblasts, neurons, endothelial cells, and epithelial cells and which of these participate ("donate" or "uptake" exosomes) in this process needs to be clarified.

Overall the study by Lobb provides important new information on the potential role of exosomes in transferring aspects of the malignant phenotype, particularly those associated with EMT and the role of ZEB1. For the long term, we will need to determine in patients, how important to the behavior of each patient's tumor is the presence of such exosomal transfer, what is the best way to diagnose its presence and can this exosomal transfer be a target for cancer prevention and/or therapy?

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Footnote

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