Acquisition and dissemination of multidrug resistance in cancer *via* microparticles

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Background: A major obstacle to the successful treatment of cancer is the acquisition of multi-drug resistance (MDR), a unique drug resistance in which tumors display cross-resistance to a wide range of unrelated drugs. MDR in cancer cells is typically caused by overexpression of efflux transporters constituting the ATP Binding Cassette Superfamily, of which P-glycoprotein (P-gp) and the Multidrug Resistance Associated protein (MRP1) are the most prominent. These transporters with their remarkable efflux capacity maintain sublethal intracellular drug concentrations, effectively rendering cancer cells treatment unresponsive.

The cellular regulation of these transporters was initially known to occur either pre- or post-transcriptionally. However, we recently discovered a novel non-genetic pathway of MDR acquisition in which microparticles (MPs) provide the vehicle for intercellular transfer of functional P-gp from multidrug resistant donor cells to drug sensitive recipient cancer cells.

Objective: The current study investigated the role of regulatory nucleic acids contained within the MP cargo in the acquisition and regulation of traits in recipient cells.

Methods and Results: MPs isolated from donor MDR cells, VLB_{100} (MDR^+) were co-cultured with drug-sensitive CCRF-CEM (MDR^-) cells for 4 h to allow for MP binding and P-gp transfer. The MP localisation on the cell surface and internalisation in recipient cells was visualised using confocal imaging. The acquisition of fully functional P-gp following MP transfer was established by flow cytometry following direct immunolabeling and by assessing Rhodamine 123 dye exclusion.

Using quantitative RT- PCR the MPs were observed to incorporate and transfer transporter transcripts including those for *ABCB1* and *ABCC1*. We observed a significant 218 fold increase and 30% decrease in *ABCB1* and *ABCC1* mRNA respectively in recipient cells following MP coculture, the resulting phenotype being reflective of that observed in the donor cell population. In examining a potential contribution by regulatory nucleic acids towards this differential profile in recipient cells, we identified *micro-RNAs* as key mediators in this pathway.

Conclusions: These findings serve to further our understanding of the intercellular pathway regulating trait acquisition in cancer cell populations and provide a basis for the development of alternative treatment strategies targeting the emergence of MDR in cancer.

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