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Abstract PR08: Microparticles derived from drug-resistant cells regulate miR-503 and PYK2 to promote migration and invasion in breast cancer

Joyce Gong, Frederick Luk, Ritu Jaiswal, and Mary Bebawy

Author Affiliations

Author Affiliations

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Abstract

Introduction: Drug resistance and metastatic spread are two of the most malicious aspects of cancer progression. Microparticles (MPs) have previously been implicated in the spread of these phenotypes independently. We now demonstrate that these two characteristics are linked, with the MP-mediated acquisition of drug resistance correlating with the emergence of an enhanced metastatic capacity. In this way, MPs serve as a conduit between drug resistance and metastasis. Therefore, addressing the impact of MPs may be a means of managing both of these deleterious aspects simultaneously. This makes MPs a significant and viable target in the management of cancer.

Methods and results: We used microarray analysis to identify regulatory microRNAs (miRNAs) contributing to the dissemination of the metastatic trait in our cancer model. *miR-503* was downregulated in recipient cells following coculture with MPs isolated from drug resistant cells. This was inversely associated with metastatic capacity, as demonstrated in wound healing/scratch migration assays and Matrigel®-coated transwell invasion assays. We also found that the proline-rich tyrosine kinase 2 (PYK2) gene transcript and miRNAs associated with its regulation, were upregulated in recipient cells following co-culture with MPs derived from drug-resistant cells. Elevated PYK2 was accompanied with increased migration and invasion, with these phenotypes reversible in the presence of a pharmacological inhibitor of PYK2 phosphorylation, tyrphostin A9. However, the MP-mediated promotion of metastatic traits was not due to the direct transfer of effectors in the selectively packaged MP cargo. Rather, acquired PYK2 protein and transcripts were downstream effectors of components within the cargo itself. Therefore, the consideration of the role of MPs in trait acquisition extends beyond the direct transfer of components within the cargo to also include the transfer of intermediary regulators, resulting in alterations in the proteomic and transcriptional landscape of the recipient cells. This implicates the expanding role of MPs in the deleterious survival mechanisms of cancer pathogenesis.

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