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CD44v6-competent tumor exosomes promote motility, invasion and cancer-initiating cell marker expression in pancreatic and colorectal cancer cells

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Cancer-initiating cells (CICs) account for tumor metastatic spread, which may rely mostly on CIC exosomes (TEX) that affect host cells and can transfer CIC features into Non-CIC. The CIC marker CD44 variant isoform v6 (CD44v6) is a metastasis promoting molecule, upregulated in pancreatic CICs. I explored the contribution of cellular and TEX CD44v6 to tumor cell migration and invasion, using a CD44v6 knockdown ($CD44v6^{kd}$) as model of Non-CIC to elaborate the contribution of CIC-TEX to transfer migratory and invasive capacity.

A $CD44v6^{kd}$ in human pancreatic and colorectal cancer (PaCa, CoCa) lines was accompanied by loss of CIC characteristics including downregulation of additional CIC markers, particularly Tspan8, which aggravated the loss of CD44v6-promoted motility and invasion. Loss of motility relies on the distorted cooperation of CD44v6 and Tspan8 with associated integrins and loss of invasiveness on reduced protease expression. These deficits accounted for $CD44v6^{kd}$ cells and TEX, the composition of $CD44v6^{kd}$-TEX being severely altered. As a consequence, $CD44v6^{kd}$ TEX were not taken up by target cells, whereas CIC-TEX were readily recovered in $CD44v6^{kd}$ cells and CICs. The uptake of CIC-TEX by $CD44v6^{kd}$ cells was accompanied by partial correction of CIC marker and protease expression in $CD44v6^{kd}$ cells, which regained migratory, invasive and metastatic competence. CIC-TEX also fostered angiogenesis and expansion of myeloid cells including myeloid-derived suppressor cells, which likely is due to a direct impact of CIC-TEX on the host, fostered by CIC-TEX reprogrammed $CD44v6^{kd}$ cells.

Taken together, the striking loss of tumor progression by a $CD44v6^{kd}$ relies on the capacity of CD44v6 to cooperate with associating integrins and proteases and its promotion of additional CIC marker expression. The defects by a $CD44v6^{kd}$ are efficiently corrected by uptake of CIC-TEX.