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Surface glycocalyx and glypican-1 mediate tumor cell metastasis

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The surface proteoglycan/glycoprotein layer (glycocalyx) on tumor cells has been associated with cellular functions that can potentially enable invasion and metastasis. In addition, aggressive renal carcinoma cells (SN12L1) with high metastatic potential have enhanced invasion rates compared to low metastatic (SN12C) cells in response to interstitial flow stimuli *in vitro*. Our previous studies suggest that heparan sulfate (HS) and hyaluronic acid (HA) in the glycocalyx play an important role in this flow mediated mechanotransduction and upregulation of invasive and metastatic potential. In our recent study, SN12L1 cells were genetically modified to suppress HS production by knocking down its synthetic enzyme NDST1. Using modified Boyden chambers with defined interstitial flow, we showed that flow-enhanced invasion is suppressed in HS deficient cells. We also examined two prominent HSPGs on renal carcinoma cells – glypican-1 and syndecan-1 and one prominent HA receptor – CD44. We observed higher glypican-1 levels in flow dependent SN12L1 cells when compared to SN12C cells. Caki-1 (highly metastatic) cells did not display flow-dependent invasion *in vitro* and did not display elevated glypican-1 compared to low metastatic Caki-2 cells. However we did observe significantly increased HS, HA, syndecan-1 and CD44 in Caki-1 compared to Caki-2 cells suggesting an alternative mechanism for reported higher metastatic rates in these cells. All of our data are consistent with the hypothesis that glypican-1 is the core protein responsible for flow sensing in metastatic cancer cells. This is also consistent with observations in endothelial cells. To assess the ability of tumor cells to metastasize *in vivo*, parental or HS knockdown SN12L1 cells expressing fluorescent reporters were injected into kidney capsules in SCID mice. Histological analysis confirmed that there was a large reduction (95%) in metastasis to distant organs by tumors formed from knockdown cells compared to control cells with intact HS. The reduction was even greater (98%) in lungs where most of the metastases from the control cells were observed. The ability of these knockdown cells to invade surrounding tissue was also impaired. The substantial inhibition of metastasis and invasion upon reduction of HS suggests an active role for the tumor cell glycocalyx and glypican-1 in tumor progression.

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