

PODOCALYXIN AS A PROGNOSTIC MARKER AND TARGET FOR MONOCLONAL ANTIBODY THERAPY IN CARCINOMA

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In kidney podocytes and other tissues, podocalyxin acts as an anti-adhesive surface protein to promote the formation of lumens and reduce intra- and inter- cellular adhesion. Podocalyxin is normally expressed on vascular endothelia, a sub-set of neurons and hematopoietic stem cells and, at much lower levels, on epithelial cells specialized in forming ducts and tubes in several tissues including breast, kidney and pancreas. However, in neoplastic disease, podocalyxin is highly expressed by tumor cells in some highly aggressive adenocarcinomas of the breast, pancreas, kidney, colon and ovary. Podocalyxin tumor expression invariably correlates with poor outcomes (overall survival and disease-free survival) and, in the case of colon cancer, identifies patients that would benefit the most from adjuvant chemotherapy. These findings indicate that podocalyxin is an important marker of prognosis and may also facilitate treatment decisions in the clinic.

To determine if podocalyxin, beyond acting as a prognostic marker, has a functional role in tumor progression and metastasis we silenced podocalyxin expression in MDA-MB-231 cells; a basal-like breast cancer cell-line that expresses high levels of endogenous podocalyxin and displays aggressive tumor growth and metastasis in xenografted mouse models. We found that deletion of podocalyxin attenuated both the growth of primary tumors and formation of distant metastases. Next, we developed a novel monoclonal antibody (PODOC1) against tumor-expressed human podocalyxin. We found that PODOC1 delays MDA-MB-231 Matrigel invasion *in vitro*. Moreover, systemic treatment of tumor-bearing mice with PODOC1 inhibits both primary tumor development and metastatic progression. These results suggest that targeting podocalyxin expression is a selective therapeutic approach for breast cancer. Importantly, because podocalyxin expression is associated with metastases in many other tumor types, podocalyxin-targeted therapies may be a widely applicable in the treatment of carcinomas.