KNOCKOUT OF COLLAGEN TYPE I IMPEDES TUMOR GROWTH AND SUPPORTS IMMUNE CELL INFILTRATION IN A MURINE MODEL OF PANCREATIC CANCER

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Background A key characteristic of cancer progression is remodeling of the extracellular matrix (ECM). This remodeling results in a tumor-specific ECM which is often of high density and rich in collagen. The high collagen density of the tumor ECM correlates with a poor prognosis in many types of cancer and with low infiltration of immune cells. The direct effects of increased intratumoral collagen on tumor progression are not yet fully understood. In this study, the role of collagen on tumor growth and immune cell infiltration were directly investigated in vivo using transgenic murine models allowing for manipulation of collagen levels.

Methods Two transgenic murine models were used to study the effects of the level of intratumoral collagen type I; a conditional knockout mouse model with decreased collagen deposition and a collagenase-resistant mouse model with increased collagen deposition. Changes in the level of collagen type I synthesis and content were demonstrated using qRT-PCR, ELISA, and histological staining. Collagen-mediated effects on immune cell infiltration were investigated using flow cytometry analyses, qRT-PCR, and immunohistochemistry. All animal studies were following institutional guidelines and were approved by the Danish Animal Experiments Inspectorate.

Results Collagen type I expression and deposition was significantly decreased in the conditional knockout mouse model. Knockout of collagen led to impeded growth of Pan02 pancreatic carcinomas. This was accompanied by increased infiltration of immune effector cells, including an increase in the amount of NK cells and an increased CD8/CD4 ratio. These results were backed up by employing the collagenase-resistant mouse model with increased collagen deposition. In these mice, tumor growth was increased and there was a higher CD4/CD8 ratio and an increased amount of immunosuppressive myeloid cells.

Conclusions The results of this study demonstrate pronounced effects of collagen on tumor progression and on the tumor immune microenvironment. The potential immunosuppressive role of collagen type I provides a rationale for extending future research in cancer immunotherapy to include focus on the ECM and in particular collagen type I.