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Title

Transglutaminase-2 mediates stromal biomechanics in colorectal cancer.

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Introduction

Increased stiffness of the tumour microenvironment is linked to aggressive cancer cell behaviour through enhanced biomechanical signalling. The protein cross-linking enzyme transglutaminase-2 (TG2) is prominently expressed in the stromal tissue surrounding cancers, and in this work the contribution of TG2 to matrix remodelling and the biomechanical properties of the tumour microenvironment in colorectal cancer (CRC) were assessed.

Materials and Methods

Organotypic models were established using primary colorectal fibroblasts and CRC cells embedded in collagen. SiRNA was used to knockout TG2, and biomechanical analysis performed using unconfined compression analysis. Models were examined by H&E and sirius red staining, and TG2 detected by immunofluorescence. TG2 expression was assessed by western blotting and flow cytometry analysis, and clinical relevance validated by analysing TG2 expression and collagen structure in tissue sections from patients with CRC.

Results

TG2 inhibited cancer cell growth in the models, and biomechanical analysis demonstrated that CRC cells induced fibroblast-mediated matrix stiffening, which was blocked by silencing TG2. Biomechanical changes were associated with observed alterations to collagen fibre structure, notably fibre thickness. Structural changes were also observed in tissues from patients with CRC, with TG2 correlating positively with thicker collagen fibres and associating with poor outcome determined by disease recurrence post-surgery and overall survival. TG2 expression was lower in cancer-associated fibroblasts compared to patient-matched normal fibroblasts, CRC cells inhibited TG2 expression in fibroblasts, and regions of reduced TG2 expression appeared to promote invasive outgrowth of CRC cells.

Discussion

This work demonstrates that TG2 contributes to the stiffer microenvironment observed in CRC. Stiffness is linked to collagen fibre thickening presumably caused by TG2-mediated cross-linking, restricting CRC growth. Notably, these matrix changes are mediated by fibroblasts in response to the presence of CRC cells, and CRC cells appear to drive down-regulation of TG2 in fibroblasts which may be a mechanism to facilitate growth and invasion. These findings are consistent with a disease model in which matrix stiffening supports an early stromal defense to invading tumour, but drives eventual poor outcome through enhanced biomechanical signalling.