

Tissue remodelling proteases as prognostic factors in colon and rectal cancer

Akademisk avhandling

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Avhandlingen baseras på följande delarbeten:

- I. Marcus Langenskiöld, Lena Holmdahl, Peter Falk, Marie-Louise Ivarsson. Increased MMP-2 protein expression in lymph node positive patients with colorectal cancer. *Int J Colorectal Dis.* 2005 May;20(3):245-52.
- II. Marcus Langenskiöld, Lena Holmdahl, Peter Falk, Eva Angenete, Marie-Louise Ivarsson. Increased TGF-beta1 protein expression in patients with advanced colorectal cancer. *J Surg Oncol.* 2008 Apr 1;97(5):409-15.
- III. Marcus Langenskiöld, Lena Holmdahl, Eva Angenete, Peter Falk, Svante Nordgren, Marie-Louise Ivarsson. Differential prognostic impact of uPA and PAI-1 in colon and rectal cancer. Submitted.
- IV. Marcus Langenskiöld, Lena Holmdahl, Eva Angenete, Peter Falk, Christina Kåbjörn-Gustafsson, Marie-Louise Ivarsson. Intestinal mucosal MMP-1 is a prognostic factor in colon cancer. In manuscript.

Abstract

Background: Colorectal cancer is the third most common cancer in Sweden and the main treatment is surgery. The TNM classification is the principal staging tool, although insufficient in identifying all patients with poor survival. The identification of molecular prognostic markers would be important in order to further aid in the identification of these patients. Components participating in the remodelling of extracellular matrix were analysed for their association with tumour progression and survival.

Methods: Patients with colorectal cancer were included in the studies during 1999-2004. Protein expression was evaluated by ELISA technique and immunohistochemistry, and related to tumour classifications. The association with cancer specific survival (CSS) was analysed by Cox proportional hazard analysis and differences between survival curves (Kaplan-Meier method) were evaluated by the Log Rank test.

Results: The expression of all measured markers were significantly higher in tumour tissue compared to tumour free mucosa. Matrix metalloproteinase-1 (MMP-1) protein expression in tumour tissue and MMP-2 expression in plasma was associated with increasing tumour stage (T-status) and lymph node metastasis in patients without distant metastatic disease. When survival data were analysed, MMP-2 in tumour tissue and MMP-1 and -9 expression in adjacent tumour free mucosa were associated with CSS in colon cancer. The association with CSS was maintained for MMP-1 in multivariate analysis also in patients without distant metastatic disease. High levels of urokinase Plasminogen Activator (uPA) expression in tumour free mucosa were associated with improved survival, but only in patients with rectal cancer. uPA expression below the chosen cut-off value identified M₀ patients with increased risk of poor survival. TGF-beta1 and PAI-1 protein expression was associated with metastatic disease and the survival analysis confirmed these results.

Discussion: Results indicate that the association of systemically measured factors with survival is due to their strong correlation with metastatic disease. These findings might reflect a generalised response to the metastatic disease. The differential association of MMP-1, MMP-9 and uPA expression with cancer specific survival in adjacent tumour free mucosa in colon and rectal cancer was unexpected. This also means that prognostic information could be available already in the preoperative setting, which could open up the opportunity to offer neo-adjuvant therapy to high-risk patients. The results suggest that the macroscopically normal mucosa in the tumour-bearing segment reflects local tumour progression, and it seems evident that important changes in the microenvironment, even remote from the tumour, are present.

Key words: extracellular matrix, survival, staging, colorectal cancer, mucosa, stroma

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